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THE DESIGN AND SYNTHESIS OF HETEROCYCLIC 1,4-DIHYDROPYRIDINES WITH POTENTIAL CALCIUM CHANNEL BLOCKING ACTIVITY

by

(C)

LINA DAGNINO

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN PHARMACEUTICAL SCIENCES (Medicinal Chemistry)

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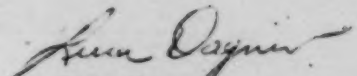

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E. E. Knaus
Supervisor

Date: April 19, 1985

To Graciela, Nicolo,

Aldo and Sudhir

ABSTRACT

A series of 2,6-dimethyl-1,4-dihydropyridines analogues of nifedipine, was synthesized to investigate their activity as calcium channel inhibitors. Several substituents were introduced at the 3-, 4- and 5-positions of the 1,4-dihydropyridine ring.

2,6-Dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridines (30-57,96-98) with identical and non-identical C-3 and C-5 substituents (*viz.* alkoxycarbonyl, nitrile and nitro groups) were synthezised by the Hantzsch condensation of 2-(3-,4-)pyridinecarboxaldehyde with alkyl acetoacetates and/or aminocrotonate, aminocrotononitrile, or 1-nitro-2-propanone.

Some 1,4-dihydropyridines selected from the previous group were subjected to reduction conditions using sodium borohydride and alkyl(aryl)chloroformates at -65°C, to afford the corresponding 2,6-dimethyl-4-{3'-(4'-)-[N-alkoxycarbonyl-1',2'-(1',6'-)-dihydropyridyl]} -1,4-dihydropyridines (58-89).

Dimethyl and diethyl 2,6-dimethyl-4-[2'-(3'-,4'-)-pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates (30,34,38,42,46,50) were quaternized with iodomethane and subsequently reduced with sodium borohydride at 0°C to yield the corresponding 4-{2'-(4'-,5'-)-[N-methyl-1',2',3',6'-tetrahydropyridyl]} -1,4-dihydropyridines 90-95.

A number of the compounds prepared were tested for inhibitory effect on guinea pig ileal longitudinal muscle contraction elicited by cis-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (CD). Inhibition of contraction of this smooth muscle may be indicative of calcium antagonistic properties of the compounds tested.

None of the analogues tested was as potent as nifedipine. Potency was dependent on the substituents present at the 3-, 4- and 5-position of the 1,4-dihydropyridine ring.

One compound, methyl 2,6-dimethyl-3-nitro-4-(3'-pyridyl)-1,4-dihydropyridine-5-carboxylate (97) promoted contraction of the guinea pig ileal longitudinal muscle at doses in the 10^{-3}M range.

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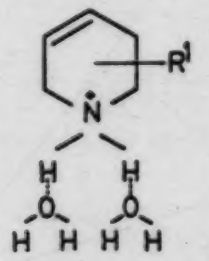
I. INTRODUCTION

A. *1,2,3,6-Tetrahydropyridines*

Physical and Spectroscopic Properties

1,2,3,6-Tetrahydropyridines 1 are basic compounds with pKa values around 9.5. Those substituted at nitrogen (2) are weaker bases, presumably because the stabilizing effect of solvation increases with the number of N-H bonds in the molecule[1] as depicted below.



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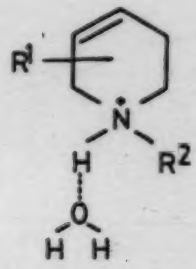


2

R^1	pKa
5-CH_3	10.17
4-CH_3	10.29
4-iPr	10.36

R^1	R^2	pKa
H	CH_3	9.2
4-CH_3	CH_3	9.49
5-CH_3	CH_3	9.29
6-CH_3	CH_3	9.43

The decreased basicity of 1,2,3,6-tetrahydropyridines relative to piperidine (pKa = 10.5) is due to the electron-attracting effect of the double bond at the C4-C5 position.

Mass spectrometry showed that the fragmentation of 1,2,3,6-tetrahydropyridines was primarily determined by the allylic enamine system[3].

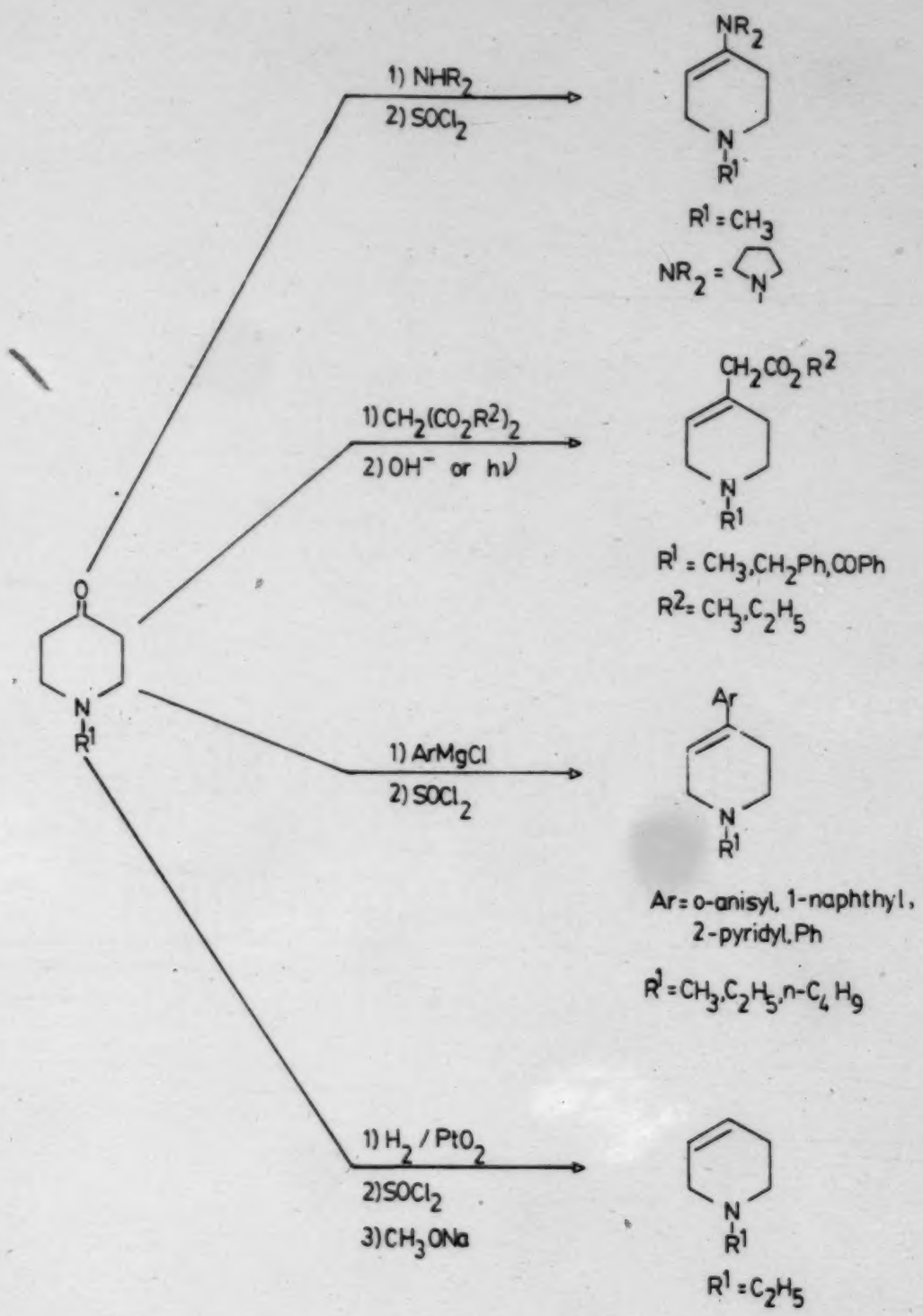
^{1}H nmr chemical shifts range between δ 5.2 and 5.6 for the vinylic hydrogen atoms. Protons vicinal to nitrogen exhibit chemical shifts between δ 0.9 and 2.6. Hydrogen atoms at C-6 appeared at lower field than those at C-2 due to the deshielding effect of the double bond[3]. The ir spectra exhibited bands in the 1650-1685 cm^{-1} range, due to C=C stretching vibrations. The uv spectra showed absorptions in the 230-290 nm region[3,4].

Synthetic Methods

1,2,3,6-Tetrahydropyridines can be prepared from piperidones by a variety of reactions as illustrated by Scheme I[3].

The Diels-Alder reaction of butadiene with electrophiles such as $CH_2=\overset{+}{N}Et_2$ Cl^- or $CF_3C(CN)=NH$[3] also afforded 1,2,3,6-tetrahydropyridines[3].

Perhaps the most selective and efficient method to prepare 1,2,3,6-tetrahydropyridines is the reduction of pyridinium salts with sodium borohydride($NaBH_4$) or aluminum hydride in aqueous or alcoholic solution. Other complex metal hydrides as lithium aluminum hydride (LAH) are too reactive and yielded mixtures in which piperidine products predominated. Similarly, when the reduction was carried out using electrolysis, catalytic hydrogenation or formic acid, completely saturated products were obtained[3].


1) NHR2
2) SOCl2
NR2
N
R1
R1 = CH3
NR2 =
1) CH2(CO2R2)2
2) OH⁻ or hν
CH2CO2R2
R1 = CH3, CH2Ph, COPh
R2 = CH3, C2H5
1) ArMgCl
2) SOCl2
Ar
Ar = o-anisyl, 1-naphthyl, 2-pyridyl, Ph
R1 = CH3, C2H5, n-C4H9
1) H2 / PtO2
2) SOCl2
3) CH3ONa
R1 = C2H5

SCHEME 1

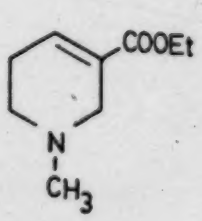
Chemical Properties

1,2,3,6-Tetrahydropyridines undergo two types of reactions, *viz.* addition to the double bond and reactions involving the ring nitrogen. The former include hydration, hydroboration, ozonolysis, addition of hydrogen and molecular halogens, epoxidation and other typical olefinic reactions.

The ring nitrogen can be alkylated or acylated by standard procedures. Mixtures of open-chained alkenes and alkynes resulted when 1,2,3,6-tetrahydropyridines were subjected to Hofmann elimination reaction conditions[3,4,6].

1,2,3,6-Tetrahydropyridines with Pharmacological Properties

1,2,3,6-Tetrahydropyridines exhibited a variety of pharmacological effects. Compounds 3 and 4 exhibited hypotensive activity[7], whereas 5[3], 6[9,10], and 7[11] were analgesics. 1,2,3,6-Tetrahydropyridines with a 4-aryl substituent, such as 8, were antipyretic and antiinflammatory agents[12].Other 1,2,3,6-tetrahydropyridines displayed muscle relaxant, antihelminthic and fungicidal activities[7].



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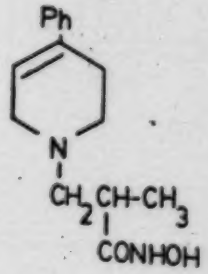

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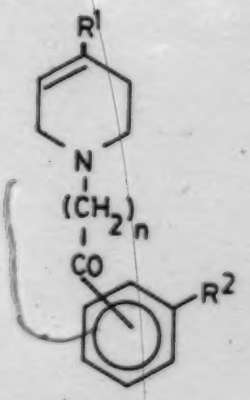
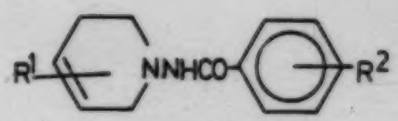


$R^1 = R^2$ = alkyl
n=1-3

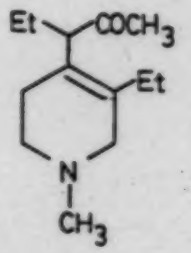
5



$R^1 = H, CH_3, OCH_3, Cl, F, NO_2$

$R^2 = H, F, OCH_3, CH_3, CH_3CO$

6



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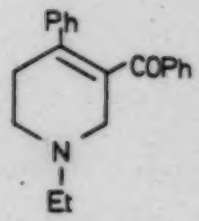


8

B. *1,2- , 1,4-, and 1,6-Dihydropyridines*

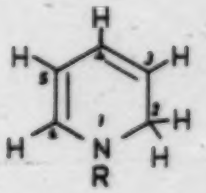
Spectroscopic Properties of 1,2- and 1,6-Dihydropyridines

The presence of conjugation in 1,2- and 1,6-dihydropyridines has resulted in uv absorptions above 200 nm. There are usually two maxima at 200-240 nm and 300-400 nm. A third band, present only in cross-conjugated analogues, appeared at 250-300 nm (1,6-isomers) or above 350 nm (1,2-isomers). Molecular extinction coefficients ranged from 3000-5000 for

simple alkyl-substituted derivatives, to 5000-25000 for analogues possessing groups that increase the conjugation of the dihydropyridine system. The nature of the substituents at C-3 and the steric interaction between groups on nitrogen and C-2 influenced the absorption characteristics of dihydropyridines. Solvent effects were relatively small, suggesting that excited states are only slightly more polar than ground states[3,12,14].

Typical bands in the ir spectra of 1,2- and 1,6-dihydropyridines appeared at 1500-1700 cm^{-1} (C=C and C=N stretching). Complex ir spectra resulted if substituents that conjugate and absorb in the same region are present. In this instance no structural assignments can be made [13]. The N-H stretching band appeared at 3000-3500 cm^{-1} for unsubstituted analogues [13,14].

^1H nmr spectra were not first order since all hydrogens in the ring coupled. Geminal methylene protons absorbed in the δ 3.0-4.5 range and are often equivalent due to planarity or rapid flipping of the ring from one conformation to another. Vinylic protons appeared between δ 4.4 and 7.6. Hydrogens attached to a double bond have larger coupling constants (J) than those attached to sp^3 carbons. Typical J values in Hz are illustrated below[16,17].



$J_{2,3}$ = 3.5 - 4.3 $J_{5,6}$ = 6.7-7.5 $J_{3,6}$ = 0.7-0.9

$J_{3,4}$ = 7.5-10.0 $J_{2,4}$ = 1.0-1.5 $J_{4,6}$ = 0.9- 1.5

$J_{4,5}$ = 3.9-5.5 $J_{3,5}$ = 0.7-1.5

Frequently hydrogens attached to nitrogen showed vicinal coupling, although this is a function of the solvent[18].

Upon electron impact 1,2-dihydropyridines expelled a hydrogen or a substituent as a radical from the C-2 position to form pyridinium ions. Mass spectra also displayed ions due to the loss of substituents on nitrogen, C-3, and C-5, and fragments arising from ring opening[13].

X-Ray studies have shown that the ring is puckered at the methylene carbon whereas the nitrogen remained planar [19,20].

Spectroscopic Properties of 1,4-Dihydropyridines

1,4-Dihydropyridines displayed uv bands in the 300 nm region. Steric, conformational and electronic features of substituents influenced the position of uv absorption bands. However, the data reported are variable and it is imposible to generalize[13,17, 21,23].

The ir spectra of 1,4-dihydropyridines are similar to those of the 1,2-isomers. 1-Alkyl-1,4-dihydropyridines exhibited a characteristic band at 1564-1575 cm^{-1} attributed to C=C and C-N vibrations[23,24].

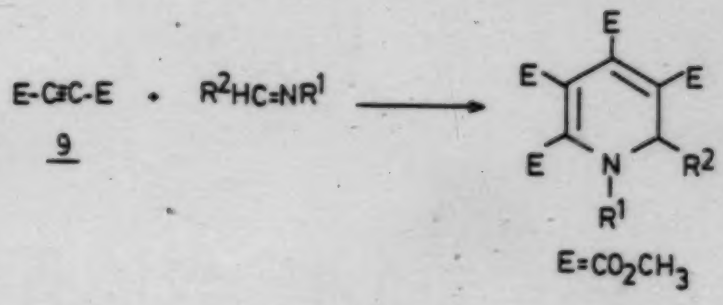
The C-4 protons of 1,4-dihydropyridines resonated at higher field than the C-2 hydrogens of 1,2-dihydropyridines[17]. Typical chemical shifts for hydrogens at C-3(C-5) and C-2(C-6) are δ 4.5 and 6.3, respectively. The J values for olefinic hydrogens ranged between 1.4 and 9Hz [23].

The most abundant fragments in the mass spectra of 1,4-dihydropyridines are due to pyridinium ions arising from loss of the C-4 substituent[26]. 1,2- and 1,4-Dihydropyridines could not differentiated by mass spectrometry because both isomers expelled the substituents at the sp^3 carbon to form pyridinium ions[27].

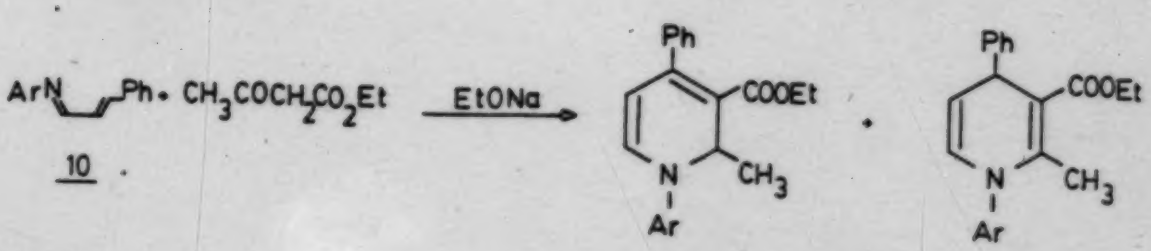
The ring conformation of 1,4-dihydropyridines in the solid state depended upon the substitution pattern. Only analogues lacking a substituent at C-4 were planar. Ring puckering increased as a consequence of greater steric interactions[28-30].

Syntheses of 1,2- and 1,6-Dihydropyridines

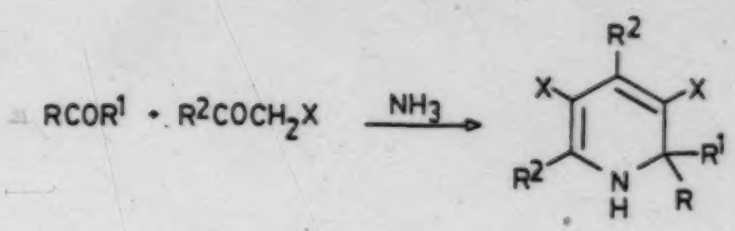
1,2-Dihydropyridines can be prepared by the cyclization reaction of dimethylacetylenedicarboxylate 9 with Schiff bases[31, 33].



The Michael condensation of ethyl acetoacetate with cis-cinnamylideneanilines 10 afforded mixtures of 1,2- and 1,4-dihydropyridines[34].



When ketones were used in place of aldehydes in the Hantzsch reaction *(vide infra)*, 1,2-dihydropyridines 11 were obtained[33].



$R=R^1=(CH_2)_4$

$R=R^1=CH_3$; $R^2=H$; $X=CH_3CO$

11

1,2-Dihydropyridines can be efficiently prepared from pyridines and pyridinium salts. These different procedures include:

a) Reduction with complex hydrides:

Electronic and steric factors determined the regiochemistry of pyridine reductions. The 1,2- and 1,6-dihydropyridines are favored kinetically. Consequently, these isomers are the major products when the nitrogen atom bears bulky or electronegative substituents as benzyl or alkoxycarbonyl groups, and also when the starting pyridine is substituted at C-4[3].

Lithium aluminum hydride and hydrides of similar reactivity yielded mixtures of 1,2- and 1,4-isomers, although it has been reported that diethyl-4-substituted-2,6-dimethyl-3,5-dicarboxylate pyridinium salts afforded 1,2-dihydropyridines upon treatment with LAH[34-36].

The reduction of pyridine with alkyl or arylchloroformates and sodium borohydride in methanol at -65°C or with diborane proceeded with high regioselectivity[31,33]. The products were 1,2- or 1,6-dihydropyridines. Reduction of alkylpyridinium salts with $NaBH_4$ in alkaline medium also produced 1,2-dihydropyridines [39,40]. 1,6-Dihydropyridines were obtained exclusively when nicotinamide pyridinium halides were treated with $NaBH_4$[34,41,42].

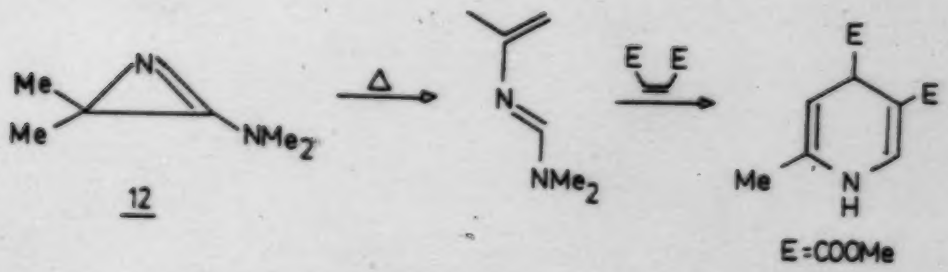
b) Addition of organometallics:

In general, addition of most nucleophiles to pyridines and pyridinium salts lead to 1,2- or 1,6-dihydropyridines. However, pyridines having electron-attracting groups at C-3 and/or C-5 gave mixtures of 1,2- and 1,4-dihydropyridines[13,14].

Nucleophilic attack by Grignard and organocadmium reagents occured regioselectively at the 2-position of pyridines and quaternary nicotinic esters[47-48]. Phenyllithium and t-butyllithium attacked pyridine and pyridinium salts specifically at C-2. Other lithium organometallics such as methyl and n-butyllithium produced mixtures of 1,2-, 1,4-, and 1,6-dihydropyridines[47-51].

Syntheses of 1,4-Dihydropyridines

The thermolysis products of 2-amino-1-azirines 12 and related systems are reported to undergo cycloaddition reactions with some electrophilic olefins to yield 1,4-dihydropyridines[37-51].

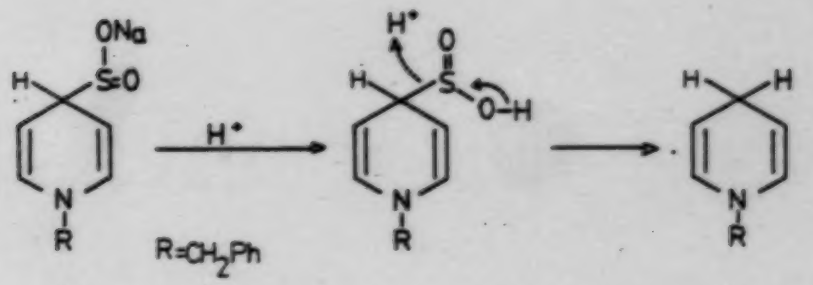


12

Nitrogen insertion into cyclopentadienes and 4H-pyrans using ammonium acetate, urea, or thiourea also afforded 1,4-dihydropyridines[14,51,59].

1,4-Dihydropyridines have been obtained by reduction of pyridine derivatives . The methods are similar to those previously described to prepare the 1,2-isomers[2,13,34]. It has been reported that reduction of pyridine-3,5-dicarboxylates using sodium cyanoborohydride afforded 1,4-dihydropyridines as the major products [39]. Lithium organocuprates and copper hydride added predominantly to the 4-position of pyridinium salts[39,40]. Grignard and organolithium reagents reacted in a similar fashion when the electrophile was a pyridine having a 3-(2-oxazoline) substituent[41], or when a catalytic amount of cuprous iodide was present[40].

Sodium dithionite and sodium hydroxymethylsulfoxylate also reduced pyridines and pyridinium compounds. The sodium sulfinate 13 has been postulated as an intermediate in the former instance and it decomposed in neutral or acidic medium to the 1,4-dihydropyridines 14[42-54].

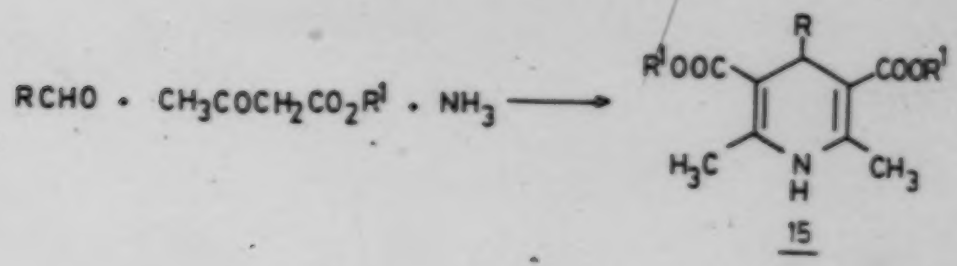


13 14

One-electron reductions with metals as sodium, sodium amalgam, zinc and aluminum[67-69], and electrolysis reactions were inefficient methods to prepare 1,4-dihydropyridines since the products obtained were usually 4,4'-tetrahydrobipyridyls[13,69,70].

To date, the best method to synthesize 1,4-dihydropyridines is the Hantzsch condensation[71]. Although this reaction only affords highly substituted derivatives, it is versatile. The mechanism is known and the yields are fair to good. Consequently, a wide variety of analogues have been prepared using the Hantzsch condensation.

The Hantzsch reaction involves the condensation of an aldehyde, a compound containing an active methylene, and a nitrogen source (Scheme II).



15

SCHEME II

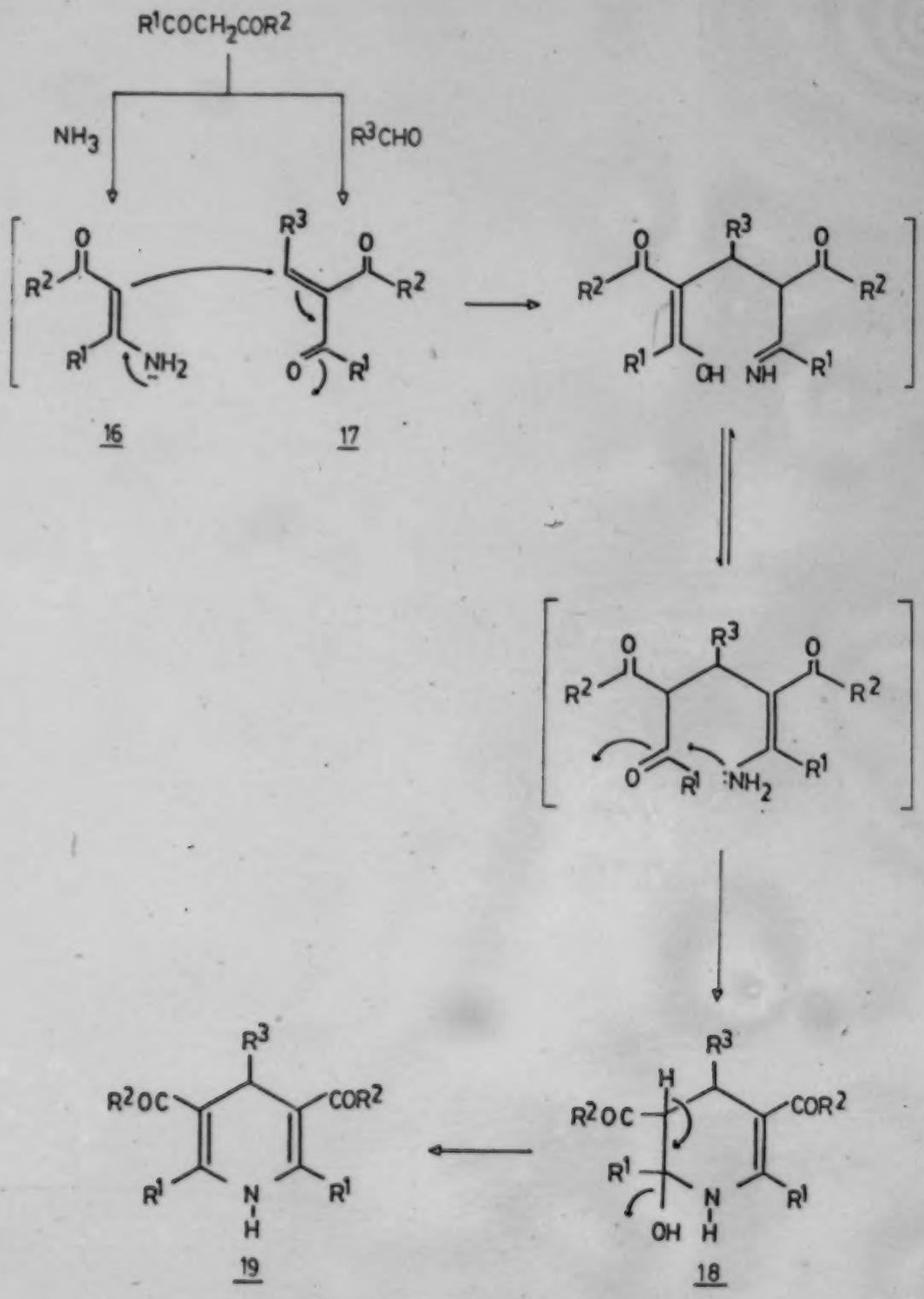
Compounds having an active methylene moiety include 1,3-dicarbonyl derivatives such as acetoacetates, 1,3- and 1,5-diketones[70-74]. Aminocrotonates[77] and aminocrotononitriles [78,79],which are putative intermediates, can be used in place of acetoacetates. These compounds simultaneously provide the nitrogen source.

β-Amino-α,β-unsaturated ketones afforded dihydropyridines lacking substituents at C-2 and C-6[30,31]. Analogues possessing a chiral carbon (C-4) are produced when two different enamines are used[32].

The source of nitrogen is usually ammonia or ammonium acetate. Utilization of primary amines is successful only when the enamine is formed first[27, 33].

The yields appeared to depend on the pH and the aldehyde used. The reaction has been carried out in both basic and strongly acidic media, resulting in controversial reports regarding the effect of pH[34,37]. Steric and electronic features of the substituents in the aldehyde appear to be important, however no systematic investigation has yet been reported[33].

The mechanism proposed for the Hantzsch reaction [33,37] involved (i) formation of a β-amino-α,β-unsaturated carbonyl derivative 16 and an alkylidene (arylidene)-1,3-dicarbonyl compound 17, (ii) Michael addition of 16, and (iii) cyclization to the tetrahydropyridine 18. The 1,4-dihydropyridine 19 is obtained by dehydration of 18 (Scheme III).

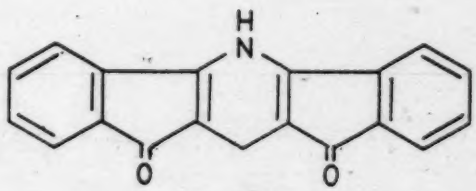


SCHEME III

Chemical Properties of Dihydropyridines

The reactions dihydropyridines undergo are dictated by the enamine systems. Delocalization of the nitrogen lone pair occured only when electron-withdrawing, unsaturated substituents are present[13].

Aromatization of dihydropyridines can be achieved with a variety of reagents such as nitrous, nitric or chromic acid, potassium ferricyanide, sulfur, pyridine N-oxide, palladium catalyst, hydrogen peroxide, silver nitrate, iodine, N-bromosuccinimide, cupric ion, oxygen, and air[17,33,76,98-99]. Occasionally, the 4-substituents of 1,4-dihydropyridines were eliminated [100]. Some analogues such as 20 resisted dehydrogenation [101,102]. Hydrogen transfer has been extensively studied for nicotinamide adenine dinucleotide (NADH) and other non-enzymatic systems [13,14,103,104].

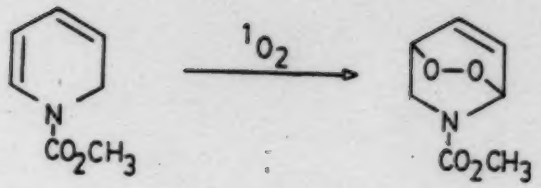


20

The disproportionation of 1,2- and 1,4-dihydropyridines yielded pyridines and 1,4,5,6-tetrahydropyridines[71,52,105], whereas hydrogenation afforded piperidines and 1,4,5,6-tetrahydropyridines[13].

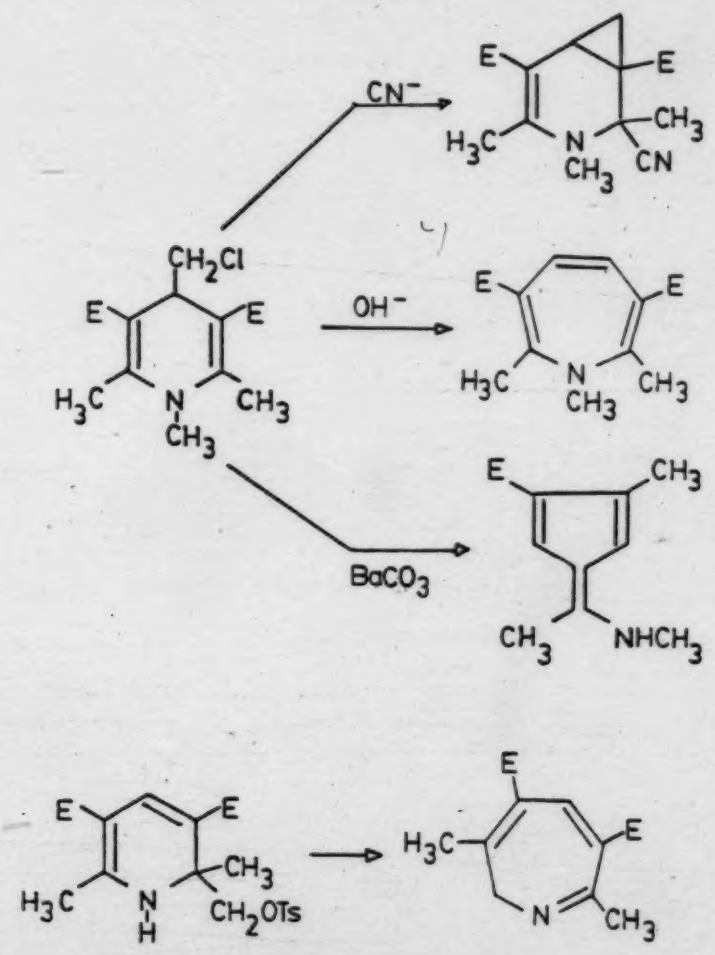
Water added to dihydropyridines under acidic conditions to yield hydroxytetrahydropyridines[106]. Similar reactions have been reported with methanol[107], hydrogen chloride[108], and thiophenol[109]. Strong bases like lithium diisopropylamide (LDA) and n-butyllithium produced vinylic carbanions that reacted with electrophiles[59,110].

Dihydropyridines can be alkylated at nitrogen using standard procedures[13]. 1,2-Dihydropyridines lacking substituents at C-3 and C-6 underwent Diels-Alder reactions[111-113] and formed endoperoxides 21 with singlet oxygen[114].



21

Dihydropyridines rearrange under various conditions as shown in Scheme IV[12,14].

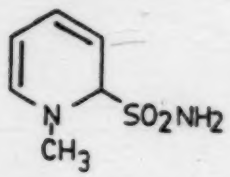


E = $COOCH_3$

SCHEME IV

Pharmacology of Dihydropyridines

1-Methyl-2-sulfanylamido-1,2-dihydropyridine 22[113] and 1-hydroxy-2-phenyl-1,2-dihydropyridine 23[116] exhibited bactericidal action.



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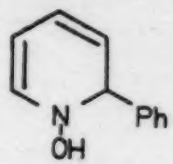


23

Nicotinamide and its 1,4-dihydro analogue are part of the coenzymes NADH and NADPH, and participate in enzymatic electron-transfer reactions. NADH and NADPH are perhaps the most widely distributed dihydropyridines in nature.

A number of Hantzsch esters which exhibit biological activity have been recently synthesized. The pharmacology of these compounds influences the physiological effects of calcium.

Calcium is present inside and outside cells, the extracellular calcium concentration being much larger[117]. Increases in cytosolic calcium trigger muscle contraction[118,119] and secretion of neurotransmitters and hormones. Calcium ions are involved in regulation of enzymatic activity[120] and control of membrane ion permeabilities[121,122].

Muscle contraction results from the cyclic attachment and detachment of cross bridges between myosin and actin, which is initiated by an increase in intracellular calcium from 0.2 μM to approximately 10μM (Fig. 1). This interaction stops upon calcium removal[123,124].

Calcium can be mobilized from extra- and intracellular sources. Their relative contributions depend primarily upon the type of tissue, stimulant and species involved.

Calcium is eliminated from the cytosol by extrusion and sequestration into the mitochondria and sarcoplasmic reticulum[125].

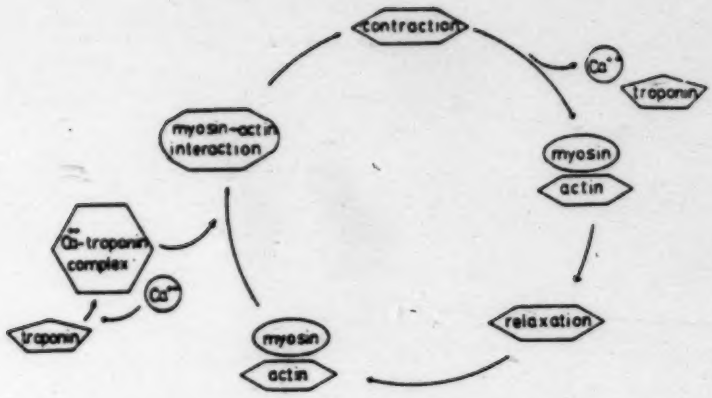


Fig 1. Mechanism of muscle contraction triggered by Ca^{2+}.

The influx of extracellular calcium is mediated by a membrane Ca^{+2}-ATPase, a Na^{+}-Ca^{+2} exchange carrier, and the slow calcium channels.

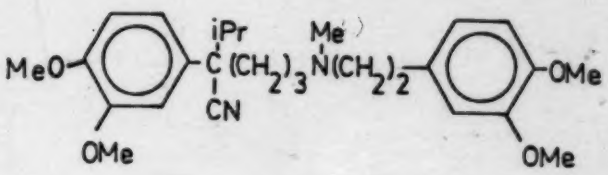
Calcium channels are pores in the cell membrane capable of transferring millions of ions per second[124]. Calcium channels seem to play an important role in effector mechanisms such as contraction, secretion, synaptic transmission, and bioluminescence, in contrast with other ion channels, like the sodium channels, whose primary function is impulse propagation[127]. The number of channels per surface unit varies from $1\mu m^{-2}$, in GH_3 pituitary tumor cells, to 30-60 μm^{-2} in snail neurons[128]. There are two kinds of calcium channels: the receptor-operated channels (ROC), and the voltage-operated channels (VOC).

The ROC's are associated with membrane receptors and are activated by a specific agonist-receptor interaction. Neurotransmitters, hormones, and drugs modulate the ROC's[126,128,129].

The VOC's are activated by membrane depolarization and are almost equally permeable to Ca, Sr, and Ba ions. The selectivity of VOC's varies in different tissues and species, suggesting that their structure is not unique. Channels can be in a resting, an open, or an inactive state. Resting and inactive channels are closed to ion transport, however the resting channel reopens in response to physiological stimuli[130]. Channel inactivation causes a decline in calcium conductance during maintained depolarization. Such inactivation may arise from membrane depolarization itself or from intracellular calcium accumulation.

Channel activation occurs with a membrane depolarization range of -40mV to +20mV[128]. Open channels can undergo saturation and blockade.

Calcium channels are preferentially blocked by the inorganic cations Mg^{+2}, Mn^{+2}, Ni^{+2}, Co^{+2}, Cd^{+2}, and La^{+3}, and organic compounds like verapamil 24, diltiazem 25, and nifedipine 26[131, 132].



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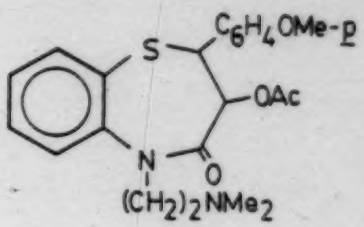

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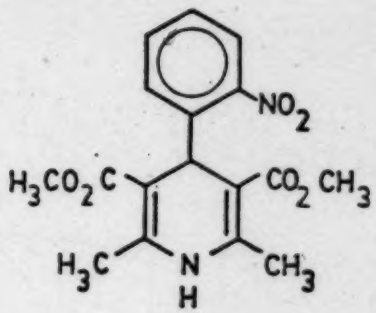
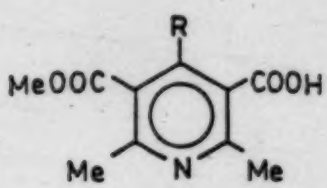


26

Nifedipine is a Hantzsch 1,4-dihydropyridine that interferes with excitation-contraction coupling of uterine, visceral, and vascular smooth muscle, and cardiac tissue (sinoatrial and atrioventricular nodes). The vasodilator effect exhibited by nifedipine is especially pronounced on coronary arteries, making it a suitable agent to treat angina pectoris and hypertension[133]. Nifedipine has also been used to treat acute pulmonary edema, asthma, cerebral vasospasm, intestinal ischemia, atherosclerosis, cardiac tissue damage, esophageal spasms and uterine contractility[134-137].

Plasma nifedipine levels have been analysed using GC/MS and HPLC techniques[138]. Oral absorption is 90%. Nifedipine is not ionized at physiological pH 92-98% of the drug is

bound to plasma proteins. Nifedipine has two major metabolites 27 and 28 and less than 0.2% is excreted unchanged[139,140]. It exhibits a few side effects such as flushing, headache and palpitations, which are primarily due to its vasodilator properties[141]. Some reports indicated that asthmatic symptoms and vasospastic angina are exacerbated after abrupt cessation of treatment[142,143].



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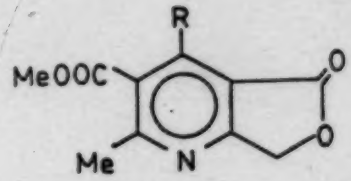


28 R=o-NO_2Ph

Many analogues of nifedipine have been prepared and tested for calcium antagonistic activity. The chemical structures and pharmacological properties of the most important derivatives are shown in Table I[144-150].

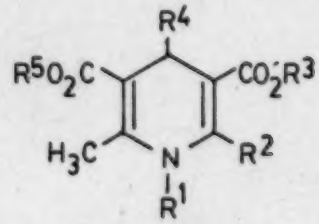
The structural features providing optimum calcium channel blocking activity for 1,4-dihydropyridines are[30,151]:

1. Minimum puckering of the 1,4-dihydropyridine ring.
2. Unsubstituted nitrogen atom.
3. Aromatic C-4 substituents.
4. Lower alkyl groups at C-2 and C-6.
5. Bulky, non-identical ester groups at C-3 and C-5.

Methyl-4-(o-trifluoromethylphenyl)-2,6-dimethyl-3-nitro-1,4-dihydropyridine -5-carboxylate 29a (BAY K 8644) and the derivative 29b (CGP 28392) are potent calcium channel activators. They exhibit a positive inotropic effect and act on central and peripheral calcium channels[152-155]. Greenberg *et al.* [153] have explained these findings by assuming that

TABLE I

Properties of Nifedipine Analogues



Name	R^1	R^2	R^3	R^4	R^5	Pharmacological Properties
Nimodipine	H	Me	$(CH_2)_2OMe$	3-NO_2-Ph	i-Pr	Extensive first pass metabolism. Metabolites are inactive or only weakly active. It improves cerebral reperfusion. The (-)-isomer is more potent
Nicardipine	H	Me	†	3-NO_2-Ph	Me	Good cerebral vasodilator. Extensive first pass metabolism. 93% of the drug is bound to plasma proteins. The (+)-isomer is 3x more potent than the (-)-isomer
Nitrendipine	H	Me	Et	3-NO_2-Ph	Me	Potent peripheral vasodilator.Inhibition of K-induced rabbit aorta contractions occurs at concentrations of 10^{-7}M for the (-)-isomer and 10^{-6}M for the (+)-isomer
Felodipine	H	Me	Et	2,3-Cl_2-Ph	Me	Promotes pronounced peripheral vasodilation. Longer duration of action than nifedipine. Positive chronotropic effects.
Flordipine	‡	Me	Et	2-CF_3-Ph	Et	Antihypertensive. Preferential vasodilation occurs in veins.
PY 200-220	H	Me	Me		i-Pr	Cerebral vasodilator. 100x more potent than nifedipine.

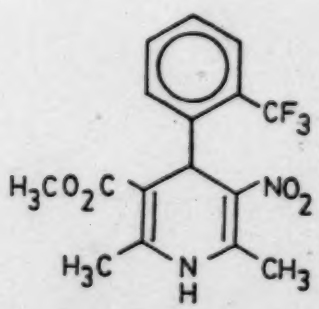
† $(CH_2)_2N(Me)(CH_2Ph)$

‡

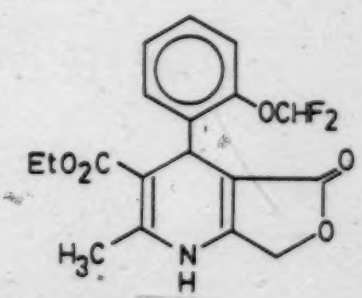
calcium antagonists act at a physiologically relevant site to promote a closed conformational state of the channel, rather than sterically hindering the passage of calcium ions. Other drugs, such as BAYK 8644, can act at the same molecular site and induce channel opening.

Tritium-labelled nifedipine analogues bind specifically to membrane preparations from cardiac, skeletal, and smooth muscle, brain and intact isolated cells[156,157]. Dihydropyridine binding sites are saturable, of high affinity (K_D =0.1-1nM), stereoselective, temperature dependent, and allosterically linked to other drug binding sites. Verapamil and methoxyverapamil (D 600) are stereoselective heterotropic inhibitors, whereas diltiazem is a positive allosteric effector. Binding does not occur without Ca^{+2}; it is inhibited by Co^{+2}, La^{+3}, and EDTA, and restored upon addition of Ca, Ba, or Sr ions[158-162]. There is a good correlation between dihydropyridine binding affinity and inhibition of K^+-induced muscle contraction, which suggests the dihydropyridine binding site is indeed the calcium antagonist receptor[163].

The receptor appears to be a membrane glycoprotein composed of three subunits with approximate molecular weights 130,000, 50,000 and 30,000. The subunits associate *via* non-covalent interactions and complex reversibly with dihydropyridines[161].



29a



29b

II. OBJECTIVES OF RESEARCH

Cardiac disease and vascular disorders are two of the primary causes of death today. Calcium antagonist and β-adrenoreceptor blocking drugs have been successfully used to treat some of these disorders. Calcium channel inhibitors have proved to be valuable drugs for the treatment and prophylaxis of arrhythmias, angina pectoris, and systemic hypertension. In addition, some calcium antagonists exert antispasmodic effects on non-vascular smooth muscle[153].

Nifedipine is one of the most potent first generation calcium channel antagonists[39]. The pharmacological activity of nifedipine is altered by changes in the substitution pattern of the 1,4-dihydropyridine ring[157]. Consequently, drugs with different potencies and tissue selectivities have been developed. This has important therapeutic implications, for example, cerebral vasodilation can be achieved without affecting the peripheral vasculature to any great extent by administering nimodipine[158] (see Table I). Structure-activity relationship (SAR) studies provide useful information for the rational design of more selective and/or potent drugs. A better understanding of physiological events involving calcium ions can also be derived from SAR studies regarding calcium channel inhibitors.

A series of nifedipine analogues was synthesized to investigate the effect of various substituents at C3, C4, and C5 upon calcium antagonistic activity.

The o-nitrophenyl ring of nifedipine was replaced by pyridyl, N-alkoxycarbonyl-1,2-(1,6-)dihydropyridyl, and N-methyl-1,2,3,6-tetrahydropyridyl substituents. This study was effected to correlate activity with different characteristics of the C-4 substituent, *viz.* , (i) presence of a heteroatom, (ii) aromaticity or degree of unsaturation, (iii) conformation, and (iv) nature and presence (or lack) of substituents.

One or both methoxycarbonyl groups of nifedipine were replaced by nitro, nitrile, and a number of alkoxycarbonyl substituents. Previous studies have shown that interactions between the C-3(C-5) and C-4 substituents influence the conformation of the 1,4-dihydropyridine ring.

Pharmacological activity correlated with planarity of the 1,4-dihydropyridine ring[39].

The pharmacological test results for the compounds prepared would provide information regarding the SAR for this class of calcium channel inhibitors.

III. RESULTS AND DISCUSSION

A number of nifedipine analogues were synthesized. These analogues are subdivided into three main classes based on the substituent attached to the C-4 position of the 1,4-dihydropyridine ring:

A. Compounds having a pyridyl ring substituent.

B. Compounds having a 1',2'-(1',6'-)dihydropyridyl ring substituent.

C. Compounds with a 1',2',3',6'-tetrahydropyridyl ring substituent.

Each class will be discussed separately.

A. *Compounds with a Pyridyl Substituent at C-4*

The nifedipine analogues in this group include:

1. 3-Alkyl-5-methyl-2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates (30-41).

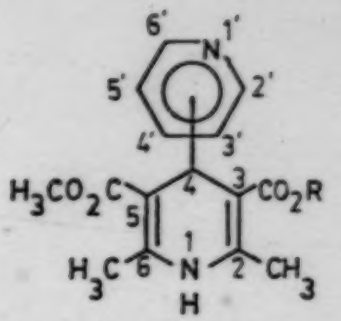
2. Dialkyl 2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates (42-53).

3. Methyl 3-cyano-2,6-dimethyl-4-[3'-(4'-)pyridyl]-1,4-dihydropyridine-5-carboxylates (54,55).

4. 3,5-Dicyano-4-[3'-(4'-)pyridyl]-1,4-dihydropyridines (56,57).

3-Alkyl-5-methyl-2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]1,4-dihydropyridine-3,5-dicarboxylates (30-41)

The 1,4-dihydropyridines 30-41 of general formula I were prepared by a modification of the Hantzsch condensation reaction[71], using a procedure reported by Iwanami and co-workers[144].

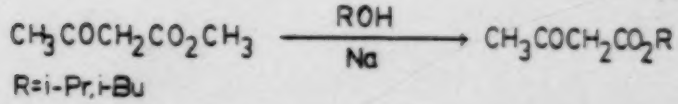


R=iPr,iBu,$(CH_2)_2NMe_2$

I

The synthesis of compounds 30-41 involved the condensation of various alkyl acetoacetates with methyl-3-aminocrotonate and 2-(3-,4-)pyridinecarboxaldehyde.

The alkyl acetoacetates were synthesized by the transesterification reaction of methyl acetoacetate and the desired alcohol (Scheme V). The reaction was carried out by mixing the required alcohol (2 mol) with methyl acetoacetate (1 mol). Sodium metal (0.3 mol) was added to produce a small amount of alkoxide anion which triggered the transesterification reaction. Dry toluene (150 mL) was added and the reaction was heated under reflux for 12-16 h.



SCHEME V

Transesterification reactions are essentially equilibria. Excess alcohol was used to drive the reaction in the product direction. The methanol formed during the reaction was removed from the mixture to avoid product conversion back to methyl acetoacetate. The most efficient

way to remove the methanol was by distilling out the azeotrope it formed with toluene. The difference between the boiling points of the azeotropic mixtures methanol:toluene and alcohol:toluene was in all cases large enough to allow efficient elimination of methanol. In this way, the transesterification reactions gave quantitative yield of products. The transesterification reaction never went to completion when methanol removal was attempted by simple distillation from the reaction mixture.

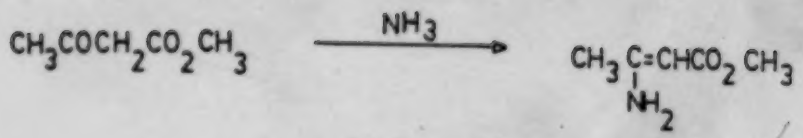
The resulting substituted acetoacetates were purified by distillation under reduced pressure.

This method failed to yield N,N-dimethylaminoethyl acetoacetate, since polymerization material was the predominant product. A modification of the procedure described by Iwanami *et al.*[144] was used to prepare N,N-dimethylaminoethyl acetoacetate. Thus, N,N-dimethylethanolamine (1 mol) was allowed to react with sodium metal (0.2 mol). When all the sodium had reacted, diketene (1 mol,50% solution in acetone) was added. The reaction mixture was heated to 70-80°C for 24h (Scheme VI). The product undergoes partial decomposition upon distillation. Therefore, the crude acetoacetate was used directly for the Hantzsch condensation.

$$(CH_3)_2N(CH_2)_2OH \xrightarrow[2)\text{diketene}]{1)Na} CH_3COCH_2CO_2(CH_2)_2N(CH_3)_2$$

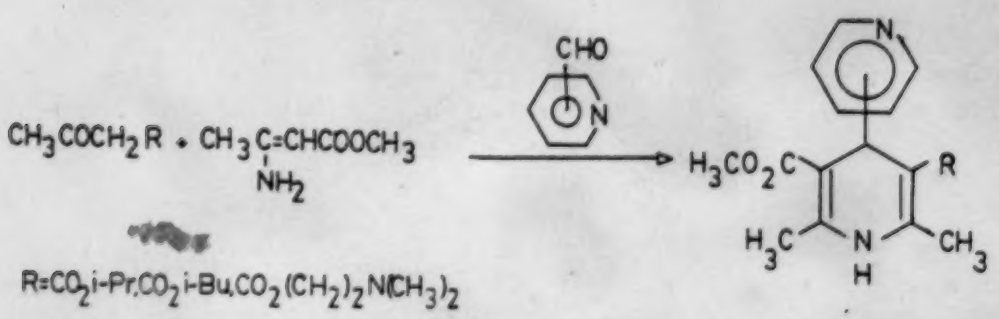
SCHEME VI

Methyl 3-aminocrotonate was synthesized by the reaction of methyl acetoacetate (1 mol) and ammonium hydroxide (3 mol) in aqueous medium at room temperature. The solid product was obtained in quantitative yield and was easily separated by filtration. Purification of the product was carried out by recrystallization from ethanol (Scheme VII).



SCHEME VII

The final step for the synthesis of compounds 30-41 was the Hantzsch condensation reaction (Scheme VIII). A typical procedure involved the reaction of i-propyl acetoacetate (1 mol), methyl 3-aminocrotonate (1 mol) and 2-pyridinecarboxaldehyde (1 mol) in ethanol (50 mL). After all the reagents were added to the mixture, the solution was heated under reflux for 12 h. The reaction mixture was allowed to cool to room temperature and poured onto crushed ice. The product separated as a solid and was filtered. Purification of the crude 1,4-dihydropyridine was carried out by flash chromatography with hexane-ethyl acetate-ethyl ether (1:1:1 v/v/v) as eluant.



SCHEME VIII

Occasionally the crude product separated as an oil or remained in solution after the reaction mixture was poured onto crushed ice. In this case, the product was extracted with dichloromethane. A solid was usually isolated after evaporation of the solvent.

The major contaminants present were dimethyl and dialkyl 1,4-dihydropyridine-3,5-dicarboxylates formed by condensation of two molecules of aminocrotonate or two molecules of alkyl acetoacetate. Aromatization of the 1,4-dihydropyridine product also occurred but the aromatic pyridine never constituted more

than 10% of the reaction product.

Some physical data for the dihydropyridines 30-41 are presented in Table II. The ir and ^{1}H nmr spectroscopic data are summarized in Table III. The N-H stretching bands appeared in the 3100-3200 cm^{-1} region. The bands due to the ester carbonyl groups were shifted to lower wavenumbers than expected and appeared at *ca.* 1700 cm^{-1} rather than 1720 cm^{-1} which may be attributed to conjugation with the 1,4-dihydropyridine ring.

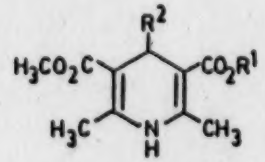
The C-2 and C-6 methyl groups appeared as ^{1}H nmr singlets in the δ 2.2 region. A singlet in the δ 5.0 region was assigned to the C-4 hydrogen atom. In this instance the deshielding effect of both the 4-pyridyl substituent and the conjugated 1,4-dihydropyridine ring is evident since the C-4 protons are deshielded relative to the majority of hydrogen atoms attached to sp^3 carbons. This may be due to the electron-withdrawing effect of the 4-pyridyl substituent and to the conjugated 1,4-dihydropyridine ring. In addition, the C-4 hydrogen is possibly located in the deshielding zone of the π-electron system of the pyridine ring and/or the 1,4-dihydropyridine ring.

The methyl groups of analogues containing one i-propoxy or i-butoxycarbonyl groups (compounds 31,32,35,36,39) showed two distinct doublets in the δ 1.5-2.0 region.The difference in the chemical shifts of the two doublets ranged from δ 0.05 to 0.2. The two ester methyl groups give rise to different signals because they are in different magnetic environments.

The magnetic non-equivalence of these ester methyl groups may be related to the conformation of the molecule. The conformation of a number of 1,4-dihydripyridine calcium antagonists have been studied by X-ray diffraction methods [30]. The information derived from crystallographic studies may provide an approximate idea of the preferred conformation of these molecules in solution. 1,4-Dihydropyridines in the solid state have a boat-type conformation. The nitrogen atom and C-4 are not planar. The torsion angles about the C-4 bond depend on interactions between the ring substituents. The aromatic ring at C-4 bisects the dihydropyridine ring. The C-2' hydrogen is located approximately above the center of the

TABLE II

Physical Data of 3-Alkyl-5-methyl-2,6-dimethyl-4-[2'(3',4')pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates



Comp.	R^1	R^2‡	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
30	Me	2'-py	239-241	77.3	$C_{16}H_{16}N_2O_4$	302	C=63.58 H=5.96 N=9.27	C=63.72 H=6.27 N=9.5
31	i-Pr	2-py	186-188	68.4	$C_{18}H_{22}N_2O_4$	330	C=65.45 H=6.66 N=8.48	C=65.37 H=6.91 N=8.24
32	i-Bu	2'-py	162-164	72.1	$C_{19}H_{24}N_2O_4$	344	C=66.28 H=6.98 N=8.14	C=65.99 H=7.14 N=8.37
33	NA†	2'-py	183-184	75.6	$C_{19}H_{11}N_3O_4$	361	C=63.16 H=7.48 N=11.63	C=63.24 H=7.51 N=11.74
34	Me	3'-py	249-250	75.6	$C_{16}H_{16}N_2O_4$	302	C=63.58 H=5.96 N=9.27	C=63.76 H=6.25 N=9.48
35	i-Pr	3'-py	176-178	63.4	$C_{18}H_{22}N_2O_4$	330	C=65.45 H=6.66 N=8.48	C=65.66 H=6.92 N=8.71
36	i-Bu	3'-py	180-182	68.2	$C_{19}H_{24}N_2O_4$	344	C=66.28 H=6.98 N=8.14	C=65.91 H=7.32 N=8.37

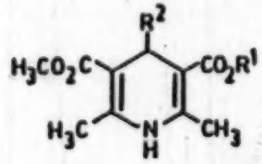
Table II cont.

37	NA†	3'-py	192-194	70.1	$C_{14}H_{11}N_3O_4$	361	C=63.16 H=7.48 N=11.63	C=63.41 H=7.27 N=11.33
38	Me	4'-py	190-192	67.2	$C_{14}H_{11}N_3O_4$	302	C=63.58 H=5.96 N=9.27	C=63.76 H=6.21 N=9.51
39	i-Pr	4'-py	199-200	73.5	$C_{15}H_{13}N_3O_4$	330	C=65.45 H=6.66 N=8.48	C=65.32 H=6.71 N= 8.63
40	i-Bu	4'-py	126-127	75.6	$C_{16}H_{15}N_3O_4$	344	C=66.28 H=6.98 N=8.14	C=66.13 H=7.16 N=8.34
41	NA†	4'-py	144-145	67.1	$C_{14}H_{11}N_3O_4$	361	C=63.16 H=7.48 N=11.63	C=63.40 H=7.27 N=11.96

† NA: 2-(N,N-dimethylamino)ethyl
‡ 2'-py: 2'-pyridyl; 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl

TABLE III

Spectroscopic Data for 3-Alkyl-5-methyl 2,6-dimethyl-4-[2'(3',4')pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates



Comp.	R'	R''	ir, cm^{-1} (CHCl$_3$) NH	ir, cm^{-1} (CHCl$_3$) CO_2R'	^1H nmr, δ (DMSO-d_6)
30	Me	2'-py	3224	1704	2.3(s,6H,CH$_3$); 3.7(s,6H,CO$_2$CH$_3$); 5.23(s,1H,H-4); 7.1-7.8(m,3H,H-3',H-4',H-5'); 8.6(m,1H,H-6'), 8.9(s,1H,NH)†
31	i-Pr	2'-py	3160	1688	1.05,1.2(two d,J=7Hz,6H,CO$_2$CH(C<u>H</u>$_3$)$_2$); 2.2(s,6H,CH$_3$); 3.6(s,3H,CO$_2$CH$_3$); 4.9(m,1H,CO$_2$C<u>H</u>(CH$_3$)$_2$), 5.2(s,1H,H-4); 7.0-7.8(m,3H,H-3',H-4',H-5'); 8.5(d,J=5Hz,1H,H-6'); 9.47(s,1H,NH)†
32	i-Bu	2'-py	3165	1704	0.8,0.9(two d,J=6Hz,6H,CO$_2$CH$_2$CH(C<u>H</u>$_3$)$_2$); 1.8(m,1H,CO$_2$CH$_2$C<u>H</u>(CH$_3$)$_2$); 2.22(s,6H,CH$_3$); 3.62(s,3H,CO$_2$CH$_3$); 3.87(d,J=7Hz,2H,CO$_2$C<u>H</u>$_2$CH(CH$_3$)$_2$); 5.22(s,1H,H-4); 7.1-7.9(m,3H,H-3',H-4',H-5'); 8.5(m,1H,H-6'); 9.5(s,1H,NH)†
33	NAt	2'-py	3170	1704	2.0-2.16(m,14H,=C-CH$_3$,CO$_2$CH$_2$CH$_2$N(C<u>H</u>$_2$)$_2$,CO$_2$CH$_2$C<u>H</u>$_2$N(CH$_2$)$_2$); 3.36(t,J=7Hz,2H,CO$_2$C<u>H</u>$_2$CH$_2$N(CH$_2$)$_2$); 3.43(s,3H,CO$_2$CH$_3$); 5.0(s,1H,H-4); 7.16-7.5(m,2H,H-3',H-5'); 7.68-8.02(m,1H,H-4'); 8.46(d,J=5Hz,1H,H-6');9.8(s,1H,NH)†
34	Me	3'-py	3192	1672	2.2(s,6H,CH$_3$); 3.6(s,6H,CO$_2$CH$_3$); 4.9(s,1H,H-4); 7.1-7.7(m,2H,H-4',H-5'); 8.3-8.48(m,2H,H-2',H-6'); 9.02(s,1H,NH)†
35	i-Pr	3'-py	3160	1704	1.12,1.26(two d,J=7Hz,6H,CO$_2$CH(C<u>H</u>$_3$)$_2$); 2.3(s,6H,CH$_3$); 3.65(s,3H,CO$_2$CH$_3$); 5.0(m,2H,CO$_2$C<u>H</u>(CH$_3$)$_2$,H-4); 7.1-7.8(m,3H,H-4',H-5',NH†); 8.4(d,J=2Hz, of d,J=5Hz,1H,H-6'); 8.6(d,J=2Hz,1H,H-2')‡
36	i-Bu	3'-py	3160	1700	0.8,0.85(two d,J=7Hz,6H,CO$_2$CH$_2$CH(C<u>H</u>$_3$)$_2$); 1.9(m,1H,CO$_2$CH$_2$C<u>H</u>(CH$_3$)$_2$); 2.2(s,6H,CH$_3$); 3.6(s,3H,CO$_2$CH$_3$); 3.9(d,J=7Hz,2H,CO$_2$C<u>H</u>$_2$CH(CH$_3$)$_2$),5.1(s,1H,H-4); 7.1-7.9(m,3H,H-4',H-5',NH†); 8.46(d,J=2Hz of d,J=6Hz,1H,H-6'); 8.63(d,J=2Hz,1H,H-2')‡

Table III cont.

37	NAł	3'-py	3176	1688	2.2(s,6H,$CO_2CH_2CH_2N(CH_3)_2$); 2.36(s and t,J=6Hz,8H,$=C-CH_3$, $CO_2CH_2CH_2N(CH_3)_2$); 3.46(t,J=6Hz,2H,$CO_2CH_2CH_2N(CH_3)_2$); 3.56(s,3H,CO_2CH_3); 4.9(s,1H,H-4); 7.43(m,2H,H-4',H-5'); 8.4(m,2H,H-2',H-6'); 9.6(s,1H,NH)†
38	Me	4'-py	3160	1704	2.36(s,6H,CH_3); 3.7(s,6H,CO_2CH_3); 5.1(s,1H,H-4); 7.06(s,1H,NH)†; 7.36 and 7.7(two d,J=6Hz,2H,H-3',H-5'); 8.53 and 8.7(two d,J=6Hz,2H,H-2',H-6')
39	i-Pr	4'-py	3160	1704	1.15,1.25(two d,J=7Hz,6H,$CO_2CH(CH_3)_2$); 2.38(s,6H,CH_3), 3.7(s,3H,CO_2CH_3); 5.1(m,2H,H-4,$CO_2CH(CH_3)_2$); 7.0(s,1H,NH)†; 7.28(d,J=5Hz,2H,H-3',H-5'); 8.48(d,J=5Hz,2H,H-2',H-6')‡
40	t-Bu	4'-py	3170	1704	0.86(d,J=6Hz,6H,$CO_2CH_2CH(CH_3)_2$); 1.9(m,1H,$CO_2CH_2CH(CH_3)_2$); 1.97(s,6H, $=C-CH_3$); 3.70(s,3H,CO_2CH_3); 3.8(d,J=7Hz,2H,$CO_2CH_2CH(CH_3)_2$); 5.1(s,1H,H-4); 7.1(s,1H,NH)†; 7.16-7.73(m,2H,H-3',H-5'); 8.3-8.73(m,2H,H-2',H-6')
41	NAł	4'-py	3176	1704	2.06(s,6H,$CO_2CH_2CH_2N(CH_3)_2$); 2.2(s and t,J=6Hz,8H,$=C-CH_3$,$CO_2CH_2CH_2N(CH_3)_2$); 3.3(t,J=6Hz,2H,$CO_2CH_2CH_2N(CH_3)_2$); 3.4(s,3H,CO_2CH_3); 4.76(s,1H,H-4); 7.06 and 7.5(two d,J=5Hz,2H,H-3',H-5'); 8.36 and 8.6(two d,J=6Hz,2H,H-2',H-6'); 8.9(s,1H,NH)†

ł NA: 2-(N,N-dimethylamino)ethyl
δ 2'-py: 2'-pyridyl; 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl
† Exchanges with D_2O
‡ Spectrum determined in $CDCl_3$

dihydropyridine ring. When the C-4 ring is substituted, the substituent will be directed away from the dihydropyridine ring. This minimizes the non-bonded interactions between C-3, C-4, and C-5 substituents (Fig. 2).

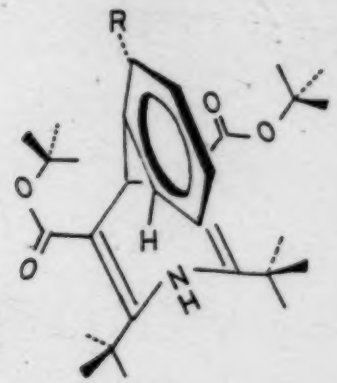


Fig. 2. Three-dimensional structure of nifedipine analogues.

There is restricted rotation about the bond joining C-4 with the aromatic ring[39]. Non-bonded interactions should be greater as the size of the C-3 and C-5 substituents is increased. When the C-3 substituent is an i-propoxycarbonyl group the probability of steric interaction between the i-propyl methyl group and the C-2 substituent increases. Non-bonded interactions between the C-4 and C-3 substituents also become more pronounced . As a result, the energy barrier for rotation about the O-$CH(CH_3)_2$ bond may increase. The alkyl chain will adopt a conformation that minimizes steric interactions. The methine hydrogen of the i-propyl ester moiety will probably be preferentially located near the C-2 substituent or near the C-4 ring. If it is near the C-2 substituent, then one of the i-propoxy methyl groups could interact with the C-4 ring. If it is positioned near the C-4 ring, then the C-2 methyl group may interact with one of the i-propoxy methyl groups. Consequently there is always a probability for steric interaction between substituents, irrespective of the conformation of the molecule . The most favored conformation would probably be influenced by the relative importance of two kinds of interactions: (i) interaction between the C-4 ring substituent and the methyl groups of the

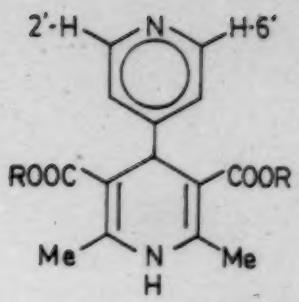
C-3(C-5) ester groups, and (ii) interaction between the C-2(C-6) methyl group and the methyl groups of the C-3(C-5) ester substituent. Therefore one of the i-propoxy methyl groups would always be in a different environment than the other, either closer to the C-2 methyl group or to the C-4 ring. Although this argument may be oversimplified conjecture, it offers an explanation for the non-equivalence of the i-propoxy methyl groups. The same rationale can be applied to explain the non-equivalence of methyl groups being part of an i-butoxycarbonyl group attached to the 3-position of the 1,4-dihydropyridine ring.

Alternatively, dual resonance signals may arise from the diastereotopic character of the two geminal methyl groups involved. When the C-3 and the C-5 substituents are different C-4 becomes chiral. However, the magnetic non-equivalence of the methyl groups of the C-3 i-propoxycarbonyl moiety is not likely to be due to the presence of a chiral C-4 atom. There are five sigma bonds between C-4 and the i-propoxycarbonyl methyl groups. In addition, nifedipine analogues possessing C-3 and C-5 i-propoxy(i-butoxy)carbonyl groups also showed dual absorptions assigned to the C-3 and C-5 ester methyl groups (*vide infra*).

Compounds 38 and 41 have a 4'-pyridyl substituent at C-4 of the 1,4-dihydropyridine ring. The ^{1}H nmr spectrum of 38 and 41 showed two different signals for H-2' and H-6'. These two protons would be expected to be equivalent due to symmetry in the 4'-pyridyl ring. However the presence of two different resonance signals indicated that the two hydrogens were in different magnetic enviroments. The non-equivalence of H-2' and H-6' may be due to restricted rotation about the C4-C4' bond which would place H-2' and H-6' in different magnetic enviroments (see discussion about molecular conformation of 4-pyridyl-1,4-dihydropyridines above). The ^{1}H nmr spectrum of 38 and 41 also showed different resonance signals for H-3' and H-5' which may be explained by the same rationale.

Dialkyl 2,6-dimethyl- 4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates (42-53)

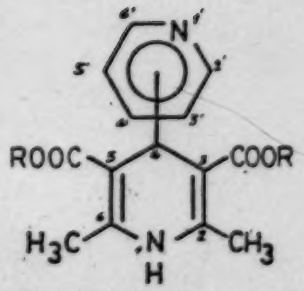
This group of compounds of general formula II was prepared following a procedure similar to that described for the synthesis of 3-alkyl, 5-methyl-1,4-dihydropyridine-



38: R=Me

41: R=$(CH_2)_2NMe_2$

3,5-dicarboxylates(30-41).



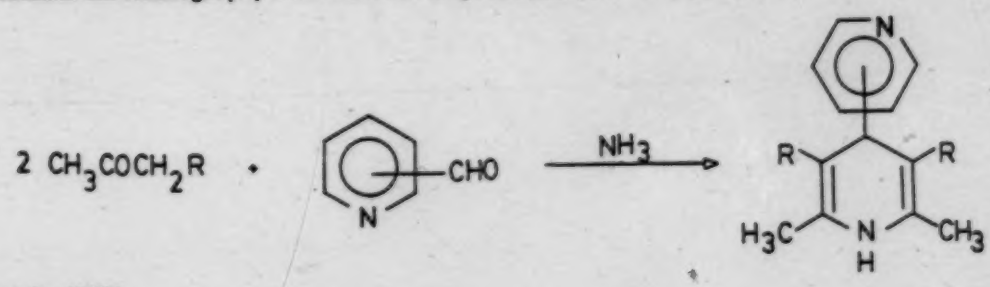
R=Me,Et,i-Pr,i-Bu,$(CH_2)_2$ $N(CH_3)_2$

II

The dihydropyridines 42-53 do not possess a chiral C-4 center since the substituents at C-3 and C-5 are identical. The analogues 42-53 were obtained when two equivalents of the alkyl acetoacetate were utilized in the Hantzsch condensation in place of one equivalent of alkyl acetoacetate and one equivalent of methyl-3-aminocrotonate. A nitrogen source must be provided in this instance, since methyl-3-aminocrotonate was not used (Scheme IX). The simplest analogue, diethyl 2,6-dimethyl-4-(2'-pyridyl)-1,4-dihydropyridine- 3,5-dicarboxylate

42 was prepared as follows: Ethyl acetoacetate (0.2 mol) was added to a solution of 2-pyridinecarboxaldehyde (0.1 mol) in ethanol (50 mL).Ammonium hydroxide (0.4 mol) was added and the mixture was heated under reflux for 12h. The reaction mixture was then poured onto crushed ice. The solid dihydropyridine obtained was filtered and recrystallized from ethanol.

The yields of 1,4-dihydropyridines 42-53 obtained in this condensation reaction were in the 75-95% range. Occasionally dialkyl 4-[2'-(3'-,4'-)pyridyl]-pyridine-3,5-dicarboxylates were also obtained. Purification of the 1,4-dihydropyridine products was then performed by column chromatography with acetone-ethyl acetate (1:9 v/v) as eluant.



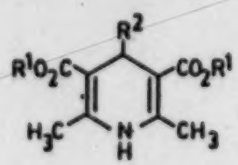
R=COOX
X=Me,Et,i-Pr,i-Bu,$(CH_2)_2N(CH_3)_2$

SCHEME IX

Some physical data for analogues 42-53 are summarized in Table IV. The spectroscopic data for compounds 42-53 (Table V) resembled those obtained for 3-alkyl-5-methyl-4-(pyridyl)-1,4-dihydropyridine-3,5-dicarboxylates(30-41). This is not surprising since both groups of compounds possess a large number of structural similarities. The diisopropyl- and diisobutyl-3,5-dicarboxylates 43,44,47,48 showed two different ^1H nmr doublets in the δ 0.8-2.0 region. Each doublet integrated for six hydrogens. Thus, there are two pairs of magnetically non-equivalent methyl groups. It is possible that the same steric effects assumed to contribute for the dual absorptions of the methyl groups for the i-propoxy and i-butoxycarbonyl substituents present in dihydropyridines 31,32,35,36 and 39 also account for the presence of the two doublets in the spectra of compounds 43,44,47 and 48.

TABLE IV

Physical Properties of Dialkyl 2,6-dimethyl-4-{2'(3',4')-pyridyl}-1,4-dihydropyridine-3,5-dicarboxylates



Comp.	R'	R'‡	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
42	Et	2'-py	194-195	89.3	$C_{19}H_{22}N_2O_4$	330	C=65.45 H=6.66 N=8.48	C=65.36 H=6.91 N=8.27
43	i-Pr	2'-py	192-193	85.6	$C_{21}H_{26}N_2O_4$	358	C=67.04 H=7.26 N=7.82	C=67.31 H=7.33 N=8.04
44	i-Bu	2'-py	152-153	88.2	$C_{23}H_{30}N_2O_4$	386	C=68.39 H=7.77 N=7.25	C=68.43 H=7.91 N=7.67
45	NA†	2'-py	205-207	93.6	$C_{31}H_{32}N_2O_4$	416	C=63.46 H=7.69 N=13.46	C=63.51 H=7.82 N=13.54
46	Et	3'py	189-191	83.7	$C_{19}H_{22}N_2O_4$	330	C=65.45 H=6.66 N=8.48	C=65.51 H=6.78 N=8.36
47	i-Pr	3'-py	213-215	86.9	$C_{21}H_{26}N_2O_4$	358	C=67.04 H=7.26 N=7.82	C=67.38 H=7.41 N= 7.63
48	i-Bu	3'-py	169-171	90.3	$C_{23}H_{30}N_2O_4$	386	C=68.39 H=7.77 N=7.25	C=68.17 H=8.02 N=7.46

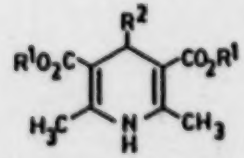
Table IV cont.

49	NA†	3'-py	152-153	77.6	$C_{17}H_{17}N_3O_4$	416	C=63.46 H=7.69 N=13.46	C=63.67 H=7.52 N=13.71
50	Et	4'-py	183-186	76.7	$C_{14}H_{11}N_3O_4$	330	C=65.45 H=6.66 N=8.48	C=65.38 H=6.43 N=8.40
51	i-Pr	4'-py	224-226	75.6	$C_{16}H_{15}N_3O_4$	358	C=67.04 H=7.26 N=7.82	C=67.22 H=7.35 N= 8.04
52	i-Bu	4'-py	167-169	78.4	$C_{17}H_{17}N_3O_4$	386	C=68.39 H=7.77 N=7.25	C=68.54 H=7.62 N=7.39
53	NA†	4'-py	161-163	62.1	$C_{17}H_{17}N_3O_4$	416	C=63.46 H=7.69 N=13.46	C=63.64 H=7.85 N=13.81

† NA: 2-(N,N-dimethylamino)ethyl
‡ 2'-py: 2'-pyridyl; 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl

TABLE V

Spectroscopic Data for Dialkyl 2,6-dimethyl-4-[2'(3',4')-pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates



Comp.	R'	R'8	ir,cm⁻¹(CHCl₃) NH	ir,cm⁻¹(CHCl₃) CO,R'	¹H nmr,δ (DMSO-d₆)
42	Et	2'-py	3160	1688	1.12(t,J=6Hz,6H,CO₂CH₂CH₃); 2.22(s,6H,CH₃); 4.02(q,J=6Hz,4H,CO₂CH₂CH₃); 5.02(s,1H,H-4); 7.0-7.8(m,3H,H-3',H-4',H-5'); 8.48(m,1H,H-6'); 8.8(s,1H,NH)†
43	i-Pr	2'-py	3192	1688	1.03,1.2(two d,J=6Hz,12H,CO₂CH(CH₃)₂); 2.2(s,6H,CH₃); 4.8(m,2H,CO₂CH(CH₃)₂); 4.96(s,1H,H-4); 6.93-7.8(m,3H,H-3',H-4',H-5'); 8.4(m,1H,H-6'); 8.66(s,1H,NH)†
44	i-Bu	2'-py	3160	1704	0.85,0.9(two d,J=7Hz,12H,CO₂CH₂CH(CH₃)₂); 1.9(m,2H,CO₂CH₂CH(CH₃)₂); 2.23(s,6H,CH₃); 3.85(d,J=7Hz,4H,CO₂CH₂CH(CH₃)₂);5.26(s,1H,H-4); 7.3-7.83(m,3H,H-3',H-4',H-5'); 8.53(m,1H,H-6'); 9.35(s,1H,NH)†
45	NAl	2'-py	3170	1688	2.16(s,12H,CO₂CH₂CH₂N(CH₃)₂); 2.26(s,6H,=C-CH₃); 2.3(t,J=7Hz,4H,CO₂CH₂CH₂N(CH₃)₂); ;3.5(t,J=7Hz,4H,CO₂CH₂CH₂N(CH₃)₂); 5.1(s,1H,H-4); 7.16-7.6(m,3H,H-3',H-4',H-5'); 8.4(m,1H,H-6'); 8.83(s,1H,NH)†
46	Et	3'-py	3192	1688	1.1(t,J=7Hz,6H,CO₂CH₂CH₃); 2.2(s,6H,=C-CH₃) 4.0(q,J=7Hz,4H,CO₂CH₂CH₃); 4.87(s,1H,H-4); 7.1-7.6(m,2H,H-4',H-5'); 8.23-8.5(m,2H,H-2',H-6'); 8.93(s,1H,NH)†
47	i-Pr	3'-py	3190	1690	0.83,0.96(two d,J=7Hz,12H,CO₂CH(CH₃)₂); 2.03(s,3H,=C-CH₃); 4.56(m,3H,CO₂CH(CH₃)₂,H-4); 7.0-7.6(m,2H,H-4',H-5'); 8.03-8.3(m,2H,H-2',H-6'); 8.7(s,1H,NH)†
48	i-Bu	3'-py	3192	1688	0.9-0.93(two d,J=7Hz,12H,CO₂CH₂CH(CH₃)₂); 1.96(m,2H,CO₂CH₂CH(CH₃)₂; 2.35(s,6H,=C-CH₃); 3.9(d,J=6Hz,4H,CO₂CH₂CH(CH₃)₂); 5.13(s,1H,H-4); 7.1-7.86(m,3H,H-4',H-5',NH†); 8.5(d,J=2Hz of d,J=5Hz,1H,H-6'); 8.7(d,J=2Hz,1H,H-2')
49	NAl	3'-py	3176	1704	2.03(s,12H,CO₂CH₂CH₂N(CH₃)₂); 2.2(s and t,J=6Hz,10H,=C-CH₃, CO₂CH₂CH₂N(CH₃)₂); 3.3(t,J=6Hz,4H,CO₂CH₂CH₂N(CH₃)₂, 4.7(s,1H,H-4); 7.23(m,2H,H-4',H-5'); 8.2(m,2H,H-2',H-6'); 8.85(s,1H,NH)†

Table V cont.

50	Et	4'-py	3192	1680	1.13(t,J=7Hz,6H,CO$_2$CH$_2$CH$_3$); 2.33(s,6H,=C-CH$_3$); 4.1(q,J=7Hz,4H,CO$_2$CH$_2$CH$_3$); 4.93(s,1H,H-4); 7.13-7.33(m,2H,H-3',H-5'); 8.5-8.7(m,2H,H-2',H-4'); 9.1(s,1H,NH)†
51	i-Pr	4'-py	3190	1688	0.86(d,J=6Hz,12H,CO$_2$CH(CH$_3$)$_2$); 2.13(s,6H,=C-CH$_3$); 4.3(s,1H,H-4); 4.8(m,J=6Hz,2H,CO$_2$CH(CH$_3$)$_2$); 7.3(d,J=6Hz,2H,H-3',H-5'); 8.4(d,J=6Hz,2H,H-2',H-6'); 9.0(s,1H,NH)†
52	i-Bu	4'-py	3160	1704	0.86(d,J=7Hz,12Hz,CO$_2$CH$_2$CH(CH$_3$)$_2$), 1.9(m,2H,CO$_2$CH$_2$CH(CH$_3$)$_2$); 2.36(s,6H,=C-CH$_3$); 3.83(d,J=6Hz,4H,CO$_2$CH$_2$CH(CH$_3$)$_2$); 5.1(s,1H,H-4); 7.13-7.4(m,3H,H-3',H-5',NH†); 8.33-8.6(m,2H,H-2',H-6')‡
53	NA‖	4'-py	3160	1704	2.1(s,12H,CO$_2$CH$_2$CH$_2$N(CH$_3$)$_2$); 2.26(s and t,J=6Hz,10H,=C-CH$_3$, CO$_2$CH$_2$CH$_2$N(CH$_3$)$_2$); 3.4(t,J=6Hz,4H, CO$_2$CH$_2$CH$_2$N(CH$_3$)$_2$); 4.83(s,1H,H-4); 7.16 and 7.6(two d,J=5.5Hz,2H,H-3',H-5'); 8.46 and 8.7(two d,J=5.5Hz,2H,H-2',H-6'); 8.96(s,1H,NH)†

§ 2'-py: 2'-pyridyl; 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl
‖ NA: 2-(*N*,*N*-dimethylamino)ethyl
‡ Spectrum determined in CDCl$_3$
† Exchanges with D$_2$O

Pharmacological Activity of Dialkyl(3-alkyl-5-methyl-) 2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates (30-53)

A number of selected 3,5-dialkyl (alkyl,methyl) 2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates were tested to investigate their inhibitory effects upon smooth muscle contraction.

The pharmacological tests were carried out in the research laboratory of Dr. M. Wolowyk by F. Li Kwong Ken.

The pharmacological testing was performed using guinea pig ileal longitudinal smooth muscle. This muscle was selected because it is fairly sensitive to the effects of calcium channel antagonists[160]. The tissue preparation and drug testing methods used were a modification of a procedure published by Triggle *et al.*[165]. The tissues were prepared as follows:

Male guinea pigs were sacrificed by decapitation. The intestine was removed above the ileo-caecal junction. Longitudinal smooth muscle segments (length=2 cm) were mounted under a resting tension of 300-400 mg. The segments were equilibrated for 1 h in a physiological saline solution of the following composition (mM): NaCl:137; $CaCl_2$:2.6; KCl:5.9; $MgCl_2$:1.2; glucose:11.9, buffered by Hepes-NaOH to pH 7.4. The bath was oxygenated (100% O_2) and maintained at 37°C. A solution change was made every 15 min.

Two successive control contractions were elicited at 15-min intervals with 10^{-7}M cis-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (CD). The mean of the two isometric contractions was taken as the 100% value for the tonic component of the response. The muscle was washed with Hepes physiological solution and was allowed to reequilibrate.

Although calcium channel inhibitors act preferentially on voltage operated channels (VOC's)[131,133], they exhibit comparable inhibitory effects on contractile responses of guinea-pig ileal longitudinal muscle elicited by agonists such as CD and by depolarization[166]. CD is a selective muscarinic agonist equipotent with acetylcholine[167]. A concentration of $5X10^{-7}$ M CD produced maximum contraction in guinea-pig ileal longitudinal muscle[165]. The responses to CD are biphasic. There is an initial rapid phasic response followed by partial relaxation. The phasic

response may be regulated by membrane-bound calcium. The second component of the response is a tonic phase which develops more slowly. The tonic response is regulated by the free extracellular calcium concentration [163] (Fig. 3). In the presence of calcium channel inhibitors tonic responses disappear more rapidly than phasic responses: 52.3% of the phasic and 0.6% of the tonic response to $5X10^{-7}$ CD remain after 30 sec [165].

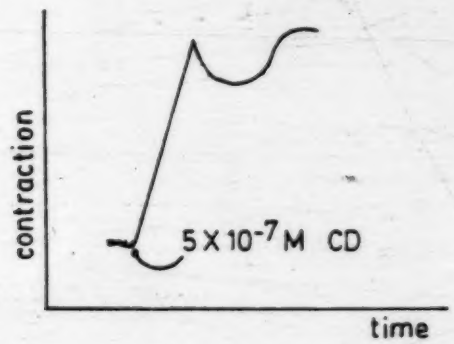


Fig. 3. Contractile response of guinea pig ileal longitudinal muscle elicited by CD.

The calcium antagonist being tested was added 10 min before the concentration-response curve for CD was determined. The pre-incubation time was only ten minutes as it was observed that antagonism did not increase upon more prolonged exposure[166].

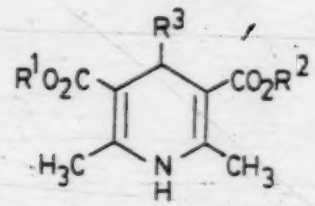
The drug-induced inhibition of the contraction was expressed as a percent of the control. The concentration of antagonist causing a 50% decrease in the contraction (ID_{50}) was determined graphically from the dose-response curves. The ID_{50} values obtained for the calcium antagonists tested are presented in Table VI. Nifedipine was also tested for use as a standard for comparison of calcium antagonistic activity. The ID_{50} of nifedipine was $1.95X10^{-9}$ M.

The following results were obtained from the pharmacological screening of nifedipine analogues having a 4-pyridyl substituent:

Substitution of the o-nitrophenyl ring of nifedipine by a 2'-, 3'-, or 4'-pyridyl ring substituent resulted in a 100-fold decrease in activity. The relative potency of the C-4 pyridyl

TABLE VI

Inhibitory activities of dialkyl 2,6-dimethyl 4- (2'(3',4')-pyridyl)- 1,4-dihydropyridine 3,5-dicarboxylates on contractile responses to CD



Comp.	R^1	R^2	R^3†	ID_{50} (M) ♂
30	Me	Me	2'-py	2.45×10^{-4} (2)
31	Me	i-Pr	2'-py	9.56×10^{-4}(3)
32	Me	i-Bu	2'-py	$(4.1\pm0.17)\times10^{-4}$ (3)
43	i-Pr	i-Pr	2'-py	$(1.25\pm0.2)\times10^{-7}$ (3)
44	i-Bu	i-Bu	2'-py	$(9.36\pm1.4)\times10^{-8}$ (4)
34	Me	Me	3'-py	3.1×10^{-4} (2)
35	Me	i-Pr	3'-py	$(9.7\pm4.6)\times10^{-8}$ (4)
46	Et	Et	3'-py	$(3.46\pm1.2)\times10^{-7}$ (3)
48	i-Bu	i-Bu	3'-py	$(1.4\pm0.6)\times10^{-7}$ (3)
38	Me	Me	4'-py	5.0×10^{-4} (2)
39	Me	i-Pr	4'-py	$(5.6\pm1.6)\times10^{-7}$ (3)
40	Me	i-Bu	4'-py	$(2.2\pm0.7)\times10^{-7}$ (3)
52	i-Bu	i-Bu	4'-py	$(5.8\pm2.1)\times10^{-7}$(3)
Nif‡	Me	Me	o-NPh	1.95×10^{-8} (3)

† 2'-py: 2'-pyridyl; 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl
o-NPh: o-nitrophenyl
‡ Nif: Nifedipine
♂ $ID_{50} \pm SD$.
No. of experiments in parentheses.

isomers was: 2'-pyridyl($ID_{50}=2.45X10^{-6}$) > 3'-pyridyl($ID_{50}=3.1X10^{-6}$) > 4'-pyridyl($ID_{50}=5.0X10^{-6}$). The decreased activity relative to nifedipine may result from a lack of substitution on the aromatic ring. Nifedipine derivatives with an ortho or a meta substituent attached to the C-4 phenyl ring are more active than those which are unsubstituted or have a para-substituent [123]. Substituents at the ortho or the meta positions cause the aryl ring to be perpendicular to the plane of the 1,4-dihydropyridine which in turn is only slightly puckered[30]. The influence of the phenyl substituents upon activity appeared to be independent of electronic character. Therefore, steric factors are likely more important[123].Compounds 30-52 do not possess a substituent on the pyridyl ring. However, the pyridyl nitrogen has an orbital with a lone electron pair. If this orbital is viewed as a substituent, the relative difference in activity for the 4-(pyridyl)-1,4-dihydropyridines may be explained in the following way. The 2'-pyridyl derivative may be similar to an ortho-substituted phenyl ring, the 3'-pyridyl analogue may resemble a meta-substituted phenyl ring and the 4'-pyridyl isomer could be equivalent to a para-substituted phenyl moiety. The steric effect that an orbital with an electron pair can induce is obviously much smaller than that of a substituent. This would result in a decreased activity relative to that of nifedipine.

Activity varied when a particular 4-substituent was held constant and the groups at C-3 and/or C-5 were substituents other than methoxycarbonyl groups. Activity was directly proportional to the size of the C-3 and/or C-5 substituents. Thus, the introduction of two i-propoxy or i-butoxycarbonyl groups in place of the initial carbomethoxy groups in the 4-(2'-pyridyl) analogues produced derivatives with a 10-fold increase in potency. Compound 44, with two i-butoxycarbonyl groups, was slightly more active than 43 which has two i-propyl ester substituents. These data agree with previous observations regarding the size of the C-3 and/or C-5 substituents attached to the 1,4-dihydropyridine ring upon activity [169,170]. The increased size of the C-3 and C-5 substituents may influence the conformation of the 1,4-dihydropyridine. The 1,4-dihydropyridine ring may tend to be more planar.The C-4 pyridyl substituent is further removed from the alcoholic portion of the C-3 and C-5 ester groups.

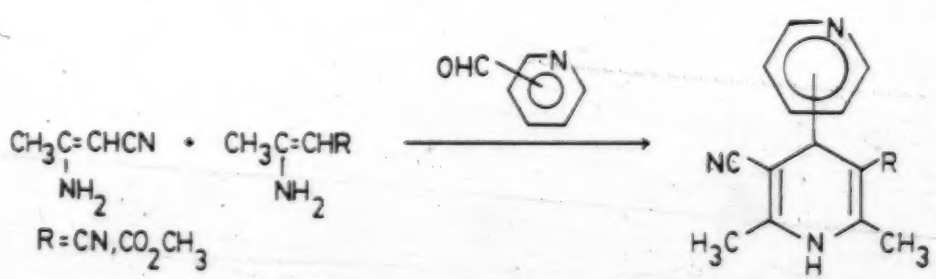
Within the same series of nifedipine analogues, the 1,4-dihydropyridines which possessed non-identical C-3 and C-5 substituents were more active than those symmetrically substituted. Thus, compound 31, having methyl and i-propyl ester groups, was more active than 43, which has two i-propoxycarbonyl groups. Similarly, 44, with two i-butyl ester groups, was less active than 32, having a methoxy and an i-butoxycarbonyl substituents at C-3 and C-5, respectively.

The same activity pattern was observed when the ester substituents were varied for compounds containing a 3'-pyridyl and a 4'-pyridyl substituent at the 4-position of the 1,4-dihydropyridine ring.

It is also interesting to note that compounds having a methoxycarbonyl and an i-propoxycarbonyl substituent were approximately equipotent to those possessing two i-butoxycarbonyl substituents. In all cases, the most active compounds had a methoxycarbonyl substituent at C-3 and an i-butoxycarbonyl group at C-5.

Methyl 3-cyano-2,6-dimethyl-4-[3'-(4'-)pyridyl]-1,4-dihydropyridine-5-carboxylates (54,56) and 3,5-Dicyano-2,6-dimethyl-4-[3'-(4'-)pyridyl]- 1,4-dihydropyridines (55,57)

Compounds 54-57 were synthesized following a procedure described by Loev [171]. These 1,4-dihydropyridines having a nitrile group in place of an ester moiety at C-3 and/or C-5, were prepared using the Hantzsch condensation described previously. 3-Aminocrotononitrile was used instead of the alkyl acetoacetate (Scheme X). A typical procedure is described below for 3,5-dicyano-4-(3'-pyridyl)-1,4-dihydropyridine 55.



SCHEME X

A solution of 3-pyridinecarboxaldehyde (0.1 mol) and 3-aminocrotononitrile (0.2 mol) in ethanol (50 mL) was heated under reflux for 24 h. The reaction mixture was poured onto crushed ice and the crude 1,4-dihydropyridine precipitated from the solution. After filtration, the product was purified by column chromatography using acetone-hexane (2:3 v/v) as eluant.

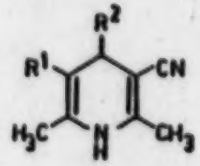
Asymmetrically substituted 1,4-dihydropyridines were synthesized using one equivalent each of methyl 3-aminocrotonate and 3-aminocrotononitrile. Thus, methyl 3-cyano-2,6-dimethyl-4-(3'-pyridyl)-1,4-dihydropyridine-5-carboxylate 54 was prepared as follows. 3-Aminocrotononitrile (0.1 mol) was added to a solution of 3-pyridinecarboxaldehyde (0.1 mol) and methyl-3-aminocrotonate (0.1 mol) in ethanol.The solution was heated under reflux during 24 h. The reaction mixture was allowed to cool to room temperature and then poured onto crushed ice. The crude 1,4-dihydropyridine separated as a solid which was filtered. Purification of the product was achieved by column chromatography using acetone-hexane (2:3 v/v)as eluant. The major contaminants present were the 3-cyano-2,6-dimethylpyridine analogues formed by oxidation of the corresponding 1,4-dihydropyridines during the reaction time. The yields of these products were acceptable, but lower than those obtained for the corresponding dialkyl 1,4-dihydropyridine-3,5-dicarboxylates.

Table VII summarizes some of the physical data for the cyano-1,4-dihydropyridines (54-57) prepared. The ir and ^{1}H nmr spectroscopic data are presented in Table VIII. The ir spectra showed N-H absorption bands in the 3200 cm^{-1} region. A band at 2200-2220 cm^{-1} was assigned to the -CN groups. Compounds 54 and 56 displayed absorption bands at 1656 and 1720 cm^{-1} respectively, which can be attributed to carbonyl stretching vibrations of the C-5 ester substituents.

The ^{1}H nmr spectra did not exhibit any unexpected spectroscopic features. The enamine proton appeared between δ 9 and 10. The C-4 proton was deshielded by the 4-pyridyl substituent and the 1,4-dihydropyridine ring. It appeared as a sharp singlet in the δ 4.5-4.7 range. The C-2 and C-6 methyl groups appeared as a singlet in the δ 2.1 region.

TABLE VII

Physical Properties of 3-Cyano-2,6-dimethyl-4-[3'(4')-pyridyl]-1,4-dihydropyridines

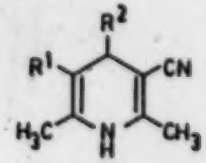


Comp.	R'	R'†	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
54	CO_2CH_3	3'-py	242-244	73.5	$C_{13}H_{13}N_3O_3$	269	C=66.91 H=5.58 N=15.61	C=66.78 H=5.36 N=15.25
55	CN	3'-py	229-230	63.2	$C_{14}H_{11}N_4$	236	C=71.19 H=5.08 N=23.73	C=71.45 H=5.32 N=23.56
56	CO_2CH_3	4'-py	195-197	63.4	$C_{13}H_{13}N_3O_3$	269	C=66.91 H=5.58 N=15.61	C=67.26 H=5.71 N=15.23
57	CN	4'-py	234-236	65.9	$C_{14}H_{11}N_4$	236	C=71.19 H=5.08 N=23.73	C=70.92 H=5.41 N=23.58

† 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl

TABLE VIII

Spectroscopic Data for 3-Cyano-2,6-dimethyl-4-[3'(4')-pyridyl]-1,4-dihydropyridines



Comp.	R¹	R'§	ir, cm⁻¹ (CHCl₃) NH	CO_2R^1	CN	¹H nmr, δ (DMSO-d_6)
54	CO_2CH_3	3'-py	3192	1656	2220	2.2(s,6H,=C-CH_3); 3.5(s,3H,CO_2CH_3); 4.7(s,1H,H-4); 7.45-8.0(m,2H,H-4',H-5'); 8.5-8.86(m,2H,H-2',H-6'); 9.8(s,1H,NH)†
55	CN	3'-py	3192	--	2220	2.1(s,6H,CH_3); 4.5(s,1H,H-4); 7.36-7.93(m,2H,H-4',H-5'); 8.5-8.7(m,2H,H-2',H-6'); 9.5(s,1H,NH)†
56	CO_2CH_3	4'-py	3192	1720	2220	2.06(s,6H,=C-CH_3); 3.5(s,3H,CO_2CH_3); 4.6(s,1H,H-4); 7.16-7.4(d,J=6Hz,2H,H-3',H-5'); 8.4-8.7(d,J=6Hz,2H,H-2',H-6'); 9.4(s,1H,NH)†
57	CN	4'-py	3190	--	2200	2.06(s,6H,=C-CH_3); 4.56(s,1H,H-4); 7.3-7.5(m,2H,H-3',H-5'); 8.6-8.8(m,2H,H-2',H-6'); 9.5(s,1H,NH)†

§ 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl
† Exchanges with D_2O

Pharmacological Activity of Methyl 3-cyano-2,6-dimethyl-[3'-(4'-)pyridyl]-1,4-dihydropyridine-5-carboxylates and 3,5-Dicyano-2,6-dimethyl-4-[3'-(4'-)pyridyl]-1,4-dihydropyridines (55-57)

The ID_{50} values for compounds 55-57 are shown in Table IX. The pharmacological test procedure was identical to that described for the dialkyl 2,6-dimethyl-4-(pyridyl)-1,4-dihydropyridine- 3,5-dicarboxylates.

Compounds 55-57 were considerably less potent than nifedipine. This shows that the presence of a nitrile group has detrimental effects upon activity. The nitrile groups may influence the conformation of the molecule. Since they are not bulky groups, their interactions with the C-4 substituents may be relatively small. Consequently, the 1,4-dihydropyridine ring may not be forced to adopt a more planar conformation to position the C-4 substituent away from the group attached at C-3 (or C-5).

B. *Nifedipine Analogues Possessing a Dihydropyridyl Substituent at C-4*

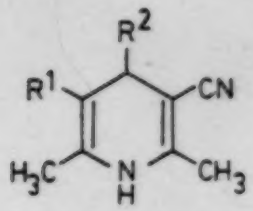
2,6-Dimethyl-4-{3'-(4'-)[N-alkoxycarbonyl-1',2'-(1',6'-)-dihydropyridyl]}-1,4- dihydropyridines (58-89)

The nifedipine analogues 30-41, having a pyridyl ring attached to the C-4 position of the 1,4-dihydropyridine moiety, are suitable precursors for the synthesis of other calcium channel inhibitors. Reduction of a variety of C-4 pyridyl substituents yielded the corresponding C-4 substituted dihydropyridyl and tetrahydropyridyl derivatives (*vide infra*). This section describes the chemical and pharmacological characteristics of nifedipine analogues having a 4-{3'-(4'-)[1',2'(1',6')-dihydropyridyl]} substituent attached to the C-4 position of the 1,4-dihydropyridine ring.

The derivatives 58-89 were prepared from the corresponding 4-(pyridinyl)-1,4-dihydropyridines using a modification of a procedure described by Fowler[37](Scheme XI). Some physical data for the compounds synthesized are summarized in

TABLE IX

Inhibitory activities of 3-cyano-2,6-dimethyl-4-[3'(4')-pyridyl]-1,4-dihydropyridines on contractile responses to CD

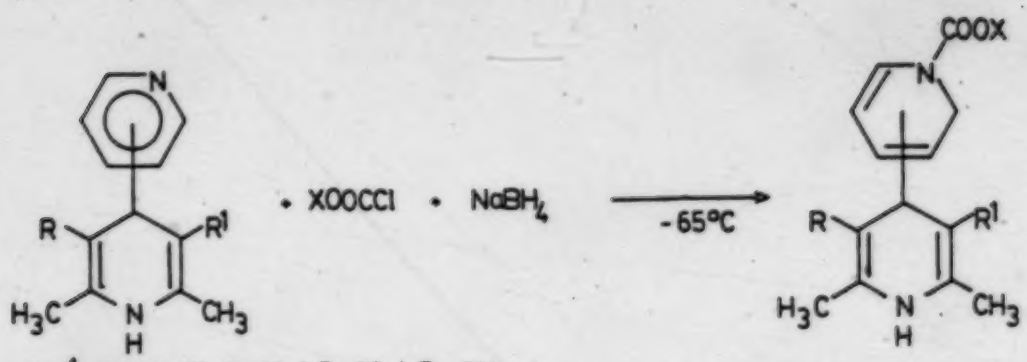


Comp.	R^1	R^2†	ID_{50}(M)δ
55	CN	3'-py	(2.8±0.2)X10^{-4}(2)
56	CO_2CH_3	4'-py	(1.3±0.5)X10^{-4}(2)
57	CN	4'-py	(1.3±0.2)X10^{-4}(2)

† 3'-py: 3'-pyridyl 4'-py: 4'-pyridyl

δ ID_{50} ± SD.
No. of experiments in parentheses.

Tables X, XII, XIV, XVI, and XVIII.



SCHEME XI

A typical synthetic procedure is described below to illustrate the synthesis of dimethyl 2,6-dimethyl-4-[4'-(N-alkoxycarbonyl-1',2'-dihydropyridyl)]-1,4-dihydropyridine-3,5-dicarboxylate 78.

Sodium borohydride (0.05 mol) was added to a solution of dimethyl 2,6-dimethyl-4-(4'-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate 38 (0.01 mol) in methanol (30 mL) precooled to -65°C. After 10 min a solution of methylchloroformate (0.015 mol) in dry ethyl ether(5 mL) was added dropwise. The reaction mixture was stirred at -65°C for 6 h and then was poured onto crushed ice. The solution was allowed to return to room temperature and the resulting solid product that separated was filtered. The crude 1',2'-dihydropyridine product was purified by flash chromatography with ethyl acetate-hexane (1:1 v/v) as eluant.

Those analogues having a t-butoxycarbonyl substituent attached to the 1'-position (nitrogen atom) of the 1',2'-dihydropyridine ring were prepared using t-butylchloroformate as the quaternization reagent. t-Butylchloroformate was prepared by adding potassium t-butoxide (0.1 mol) to a solution of phosgene (0.1 mol,12.5% sol. in benzene) in ethyl ether (40 mL) precooled at -65°C. The reaction was allowed to proceed at -65°C for 5 h and the unpurified t-butylchloroformate was used in the subsequent reduction without allowing the solution to warm up.

Reduction of dialkyl 2,6-dimethyl-4-(3'-pyridyl)-1,4-dihydropyridyl-3,5-dicarboxylates afforded mixtures of the two isomers 4-[3'-(N-alkoxycarbonyl-1',2'-dihydropyridyl)]- and 4-[3'-(N-alkoxycarbonyl-1',6'-dihydropyridyl)]-1,4-dihydropyridines. All attempts to separate the two isomers by column or thin layer chromatographic techniques failed. The ratio of 1',2':1',6'-dihydropyridine isomers was determined from the ^{1}H nmr spectrum of the mixture.

In general, the 1',2'-dihydropyridyl ring seemed to be sensitive to the water added during the isolation procedure. Attempts to reduce some of the analogues 30-41 failed and in all cases some degree of aromatization of the 1',2'-dihydropyridyl ring back to the pyridyl precursor was observed.

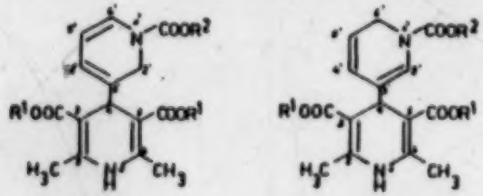
The 4-(pyridinyl)-1,4-dihydropyridines possessing a 2-(N,N-dimethylamino)ethoxycarbonyl substituent at C-3 and/or C-5 did not yield the desired 4-(1',2'-dihydropyridyl) products. The alkyl chloroformate reacted preferentially with the more basic aliphatic nitrogen to give a quaternary salt which was hydrolyzed by the solvent and in all cases the starting material was recovered unchanged. Attempts to protonate the aliphatic nitrogen with hydrogen chloride prior to quaternization of the pyridyl nitrogen with the chloroformate were also unsuccessful.

The ir and ^{1}H nmr spectra for compounds 58-91 are summarized in Tables XI, XIII, XV, XVII, and XIX. The ir spectra frequently exhibited overlapping bands for the ester and carbamate groups. These bands were generally shifted to lower wave numbers than normal due to conjugation of the ester and the carbamate groups with the dihydropyridine ring to which they are attached.

The ^{1}H nmr spectra for compounds having a C-3 and/or C-5 i-propoxy(i-butoxy)carbonyl substituent (60,64,65,68,86) indicated that the methyl groups present in the C-3 and/or C-5 ester substituent were not magnetically equivalent. This was previously observed for the parent C-4 pyridinyl derivatives (*vide supra*). The two methyl chemical shifts for $-CH(CH_3)_2$ and $-CH_2CH(CH_3)_2$ are separated by approximately δ 0.2.

TABLE X

Physical Properties of Dialkyl 2,6-dimethyl-4-[3'-{N-alkoxycarbonyl-1',2'-(1',6')-dihydropyridyl}-]-1,4-dihydropyridine-3,5-dicarboxylates



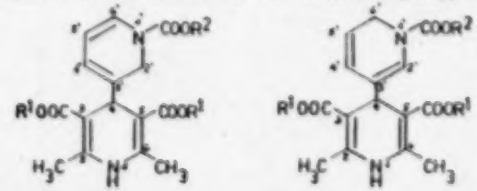
Comp.	R¹	R²	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
58	Me	Me	158-160	73.4	$C_{19}H_{22}N_2O_6$	362	C=59.67 H=6.07 N=7.23	C=59.59 H=6.26 N=7.26
59	Et	Me	115-116	75.2	$C_{21}H_{26}N_2O_6$	390	C=61.54 H=6.66 N=7.18	C=61.54 H=6.41 N=7.36
60	i-Pr	Me	151-153	68.7	$C_{23}H_{30}N_2O_6$	418	C=63.16 H=7.17 N=6.7	C=63.35 H=7.28 N=6.91
61	i-Bu	Me	138-139	75.8	$C_{25}H_{34}N_2O_6$	446	C=64.57 H=7.62 N=6.28	C=64.31 H=7.83 N=6.36
62	Me	Ph	147-149	55.8	$C_{29}H_{28}N_2O_6$	424	C=65.09 H=5.66 N=6.60	C=65.31 H=5.78 N=6.78
63	Et	Ph	162-164	57.4	$C_{31}H_{32}N_2O_6$	452	C=66.37 H=6.19 N=6.19	C=66.51 H=6.18 N=6.41
64	i-Pr	Ph	114-116	58.3	$C_{33}H_{36}N_2O_6$	480	C=67.50 H=6.66 N=5.83	C=67.23 H=6.91 N=5.59

Table X cont.

65	t-Bu	Ph	172-174	62.4	$C_{33}H_{36}N_2O_4$	508	C=68.50 H=7.08 N=5.51	C=68.24 H=6.96 N=5.78
66	Et	t-Bu	152-154	68.9	$C_{31}H_{32}N_2O_4$	432	C=63.89 H=7.41 N=6.48	C=63.71 H=7.62 N=6.42
67	i-Pr	t-Bu	148-150	74.6	$C_{32}H_{34}N_2O_4$	460	C=65.22 H=7.83 N=6.09	C=65.34 H=7.98 N=6.16
68	t-Bu	t-Bu	153-155	78.2	$C_{33}H_{36}N_2O_4$	488	C=66.39 H=8.19 N=5.74	C=66.28 H=8.34 N=5.46

TABLE XI

Spectroscopic Data for Dialkyl 2,6-dimethyl-4-[3'-[N-alkoxycarbonyl-1',2'-(1',6')-dihydropyridyl]-]-1,4-dihydropyridine-3,5-dicarboxylates



(a) (b)

Comp.	R^1	R^2	ir,cm^{-1}(CHCl$_3$) NH	CO_2R^1	NCO_2R^2	Ratio d a:b	^{1}H nmr,δ (DMSO-d$_6$)†‖
58	Me	Me	3340	1680-1710		9:7	2.3(s,12H,=C-CH$_3$)‡; 3.63(s,12H,CO$_2$CH$_3$)‡; 3.7(s,6H,NCO$_2$CH$_3$)‡; 4.16 and 4.2(two s,4H, H-2',[H-6']); 4.36(s,2H,H-4)‡;5.22(m,1H,H-5'); 5.5(d,J=5.5Hz,1H,H-4'); 5.58(m,$J_{4',5'}$ = 10.3Hz,1H,[H-5']); 5.8(d,J=10.3Hz,1H,[H-4']); 6.36(s,1H,[H-2']); 6.56(d,J=6.1Hz,1H,H-6'); 8.89(s,1H,NH); 8.98(s,1H,[NH])
59	Et	Me	3340	1700		2:1	1.18(t,J=7.2Hz,12H,CO$_2$CH$_2$CH$_3$)‡; 2.24 and 2.26 (two s,12H,=C-CH$_3$)‡; 3.71(s,6H,NCO$_2$CH$_3$)‡; 3.98-4.4(m,14H,H-2',[H-6'], H-4‡,CO$_2$CH$_2$CH$_3$‡); 5.2(m,1H,H-5'); 5.48(m,$J_{4',5'}$ =4.3Hz,1H,H-4'); 5.56(m,1H,[H-5']); 5.8(d,J=10Hz,1H,[H-4']); 6.4 and 6.42(two s,1H,[H-2']); 6.56(m,1H,H-6'); 8.8(s,1H,[NH]); 8.92(s,1H,NH)
60	i-Pr	Me	3315	1688	1704	7:3	1.23(m,24H,CO$_2$CH(CH$_3$)$_2$)‡; 2.26 and 2.28(two s,12H,=C-CH$_3$)‡; 3.74(s,6H,NCO$_2$CH$_3$)‡; 4.16-4.44(m,6H,H-2', [H-6'],H-4‡); 4.96(m,4H,CO$_2$CH(CH$_3$)$_2$)‡; 5.23(m,1H,H-5'); 5.5(m,1H,H-4'); 5.62(m,$J_{4',5'}$ =10.7Hz, 1H,[H-5']); 5.83(d,J=10.17Hz,1H,[H-4']); 6.44 and 6.46(two s,1H,[H-2']); 6.58(m,1H,H-6'); 8.74(s,1H,[NH]); 8.88(s,1H,NH)
61	i-Bu	Me	3330	1688		5:3	0.9(d,J=5.7Hz,24H,CO$_2$CH$_2$CH(CH$_3$)$_2$)‡; 1.86(m,4H,CO$_2$CH$_2$CH(CH$_3$)$_2$)‡; 2.2 and 2.22(two s,12H,=C-CH$_3$)‡; 3.3(s,6H,NCO$_2$CH$_3$)‡; 3.8(d,J=7.4Hz,8H,CO$_2$CH$_2$CH(CH$_3$)$_2$)‡; 4.06-4.28(m,4H,H-2', H-4‡); 4.4(m,2H,[H-6']); 5.16(m,2H,H-5'); 5.45(m,1H,H-4'); 5.56(m,1H,[H-5']); 5.76(m,$J_{4',5'}$ =10Hz,1H,[H-4']); 6.4(s,1H,[H-2']); 6.6(m,1H,H-6'); 8.8(s,1H,[NH]); 8.94(s,1H,NH)
62	Me	Ph	3380	1710-1730		3:1	2.24(s,12H,=C-CH$_3$)‡; 3.62(s,12H,CO$_2$CH$_3$)‡; 4.22(s,2H,H-4)‡; 4.35 and 4.41(two m,4H,H-2',[H-6']); 5.3(m,1H,H-5'); 5.54(d,J=5.5Hz,1H,H-4'); 5.64(m,1H,[H-5']); 5.84(d,J=8.8Hz,1H,[H-4']); 6.53(s,1H,[H-2']); 6.7(d,J=8.8Hz,1H,H-6'); 7.1-7.6(m,10H,NCO$_2$C$_6$H$_5$)‡; 8.9(s,1H,[NH]); 8.96(s,1H,NH)

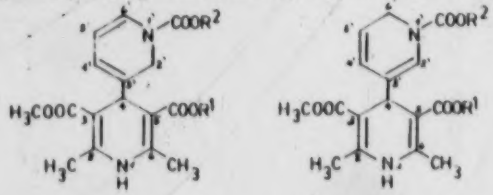
Table XI cont.

63	Et	Ph	3380	1710	1720	4:3	1.24(t,J=8Hz,12H,$CO_2CH_2\underline{CH_3}$)‡; 2.26(s,12H,=C-CH_3)‡; 3.98-4.54(m,10H,H-2',[H-6'],H-4‡,$CO_2\underline{CH_2}CH_3$‡; 5.36(m,1H,H-5'); 5.58(m,1H,H-4'); 5.68(m,$J_{4',5'}$=8.5Hz, 1H,[H-5']); 5.88(d,J=8.5Hz,1H,[H-4']); 6.62(s,1H,[H-2']); 6.8(d,J=8.5Hz,1H,H-6'); 7.18-7.6(m,10H,$NCO_2C_6H_5$)‡; 8.83(s,2H,NH)‡
64	i-Pr	Ph	3352	1704	1720	4:3	1.24(m,24H,$CO_2CH(\underline{CH_3})_2$)‡; 2.26,2.28(two s,12H,=C-CH_3)‡; 4.2-4.6(m,6H,H-2',[H-6'],H-4‡); 4.96(m,4H,$CO_2\underline{CH}(CH_3)_2$); 5.34(m,1H,H-5'); 5.56(m,1H,H-4'); 5.7(m,1H,[H-5']); 5.88(m,1H,[H-4']); 6.63(s,1H,[H-2']); 6.8(d,J=6.98Hz,1H,H-6'); 7.16-7.6(m,10H,$NCO_2C_6H_5$)‡; 9.76(s,1H,[NH]); 9.82(s,1H,NH)
65	i-Bu	Ph	3320	1664-1704		2:1	0.86(d,24H,$CO_2CH_2CH(\underline{CH_3})_2$)‡; 1.86(m,4H,$CO_2CH_2\underline{CH}(CH_3)_2$)‡; 2.2 and 2.24(two s,12H,=C-CH_3)‡; 3.79(d,J=6.4Hz,8H,$CO_2\underline{CH_2}CH(CH_3)_2$)‡; 4.21(s,2H,H-4)‡; 4.41(m,4H,H-2',[H-6']); 5.3(m,1H,H-5'); 5.44-5.72(m,2H,H-4',[H-5']); 5.8(m,1H,[H-4']); 6.38 and 6.62(two s,1H,[H-2']); 6.54 and 6.72(two d, J=6.4Hz,1H,H-6'); 7.04-7.58(m,10H,$NCO_2C_6H_5$)‡; 9.84(s,1H,[NH]); 9.96(s,1H,NH)
66	Et	t-Bu	3352	1688	1720	2:1	1.22(t,J=7.5Hz,12H,$CO_2CH_2\underline{CH_3}$)‡; 1.46(s,18H,$NCO_2C(CH_3)_3$)‡; 2.26 and 2.28(two s,12H,=C-CH_3)‡; 4.06-4.26(m,12H,H-2',[H-6'],$CO_2\underline{CH_2}CH_3$‡); 4.34(s,2H,H-4)‡; 5.17(m,1H,H-5'); 5.5(d,J=6Hz,1H,H-4'); 5.54(m,1H,[H-5']); 5.81(d,J=11Hz,1H,[H-4']); 6.38 and 6.52(two d,each overlapping with a s, 2H,H-6',[H-2']); 8.78(s,1H,[NH]); 8.89(s,1H,NH)
67	i-Pr	t-Bu	3336	1688		7:3	1.3(two overlapping d,J=7Hz,24H,$CO_2CH(\underline{CH_3})_2$)‡; 1.5(s,18H,$NCO_2C(CH_3)_3$)‡; 2.32 and 2.34(two s,12H,=C-CH_3); 4.15-4.8(m,6H,H-2',[H-6'], H-4‡); 4.9(m,4H,$CO_2\underline{CH}(CH_3)_2$‡;5.24(m,1H,H-5'); 5.56(d,J=5.4Hz,1H,H-4'); 5.6(m,1H,[H-5']); 5.85(d,J=7.7Hz,1H,[H-4']); 6.47 and 6.6 (two d,each overlapping with a s,2H,H-6',[H-2']); 8.88(s,1H,NH); 8.98(s,1H,[NH])
68	i-Bu	t-Bu	3336	1690		2:1	0.9(m,24H,$CO_2CH_2CH(\underline{CH_3})_2$)‡; 0.96(s,18H,$NCO_2C(CH_3)_3$)‡; 1.92(m,4H,$CO_2CH_2\underline{CH}(CH_3)_2$)‡; 2.3-2.36(four s,12H,=C-CH_3)‡; 3.85(m,8H,$CO_2\underline{CH_2}CH(CH_3)_2$)‡; 4.23(s,2H,H-4)‡; 4.23 and 4.47(two m,4H,H-2',[H-6']); 5.22(m,1H,H-5'); 5.54(d,J=3.8Hz,1H,H-4'); 5.6(m,1H,[H-5']); 5.86(d,J=8.9Hz,1H,[H-4']); 6.5 and 6.58 (two s,1H,[H-2']); 6.57(d,J=7.6Hz,1H,H-6'); 9.02(s,1H,NH); 9.1(s,1H,[NH])

† H-n': refers to signals due to the 1',2'-dihydropyridyl isomer(a); [H-n']: refers to signals due to the 1',6'-dihydropyridyl isomer (b)
‡ Signals common to both 1',2'- and 1',6'-dihydropyridyl isomers
d Ratio determined from integration curves of NH and [NH] singlets.
■ Assignments confirmed by double resonance experiments. All NH protons exchange with D_2O

TABLE XII

Physical Properties of 3-Alkyl5-methyl-2,6-dimethyl-4-[3'-[N-alkoxycarbonyl-1',2'-(1',6')-dihydropyridyl]]-1,4-dihydropyridine-3,5-dicarboxylates

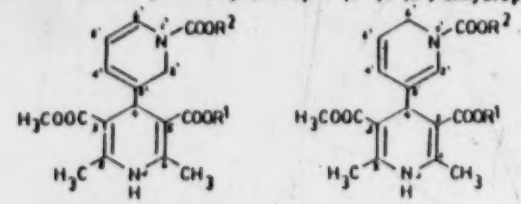


(a) (b)

Comp.	R¹	R'†	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
69	i-Bu	Me	181-183	77.8	$C_{21}H_{28}N_2O_6$	404	C=62.37 H=6.93 N=6.93	C=62.27 H=6.72 N=6.85
70	i-Bu	Ph	162-163	63.2	$C_{26}H_{30}N_2O_6$	466	C=66.95 H=6.44 N=6.01	C=66.74 H=6.78 N=6.26
71	i-Pr	t-Bu	136-138	71.9	$C_{23}H_{32}N_2O_6$	432	C=63.89 H=7.41 N=6.48	C=63.91 H=7.36 N=6.55

TABLE XIII

Spectroscopic Data for 3-Alkyl5-methyl-2,6-dimethyl-4-[3'-[N-alkoxycarbonyl-1',2'-(1',6')-dihydropyridyl]]-1,4-dihydropyridine-3,5-dicarboxylates



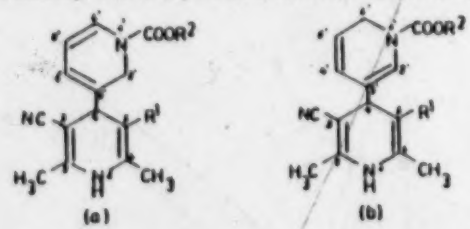
(a) (b)

Comp.	R¹	R²	ir,cm⁻¹(CHCl₃) NH	CO,R¹	NCO,R²	Ratio a:b	¹H nmr,δ (DMSO-d₆)†,■
69	i-Bu	Me	3320	1688	1704	3:1	0.92(d,J=7Hz,12H,CO₂CH,CH(CH₃)₂)‡; 1.92(m,2H,CO₂CH,CH(CH₃)₂)‡; 2.28 and 2.3(two s,12H,=C-CH₃)‡; 3.66(s,6H,CO₂CH₃) ‡; 3.72(s,6H,NCO₂CH₃)‡; 3.82(m,4H,CO₂CH,CH(CH₃)₂)‡; 4.18(broad s,2H,[H-6']); 4.24(broad s, 2H,H-2'); 4.42(s,2H,H-4)‡; 5.18(m,1H,H-5'); 5.53(d,J=5.3Hz,1H,H-4'); 5.54(m,1H,[H-5']); 5.85(d,J=9.7Hz,1H,[H-4']); 6.44(s,1H,[H-2']); 6.55(d,J=7.7Hz,1H,H-6'); 8.73(s,1H,[NH]); 8.84(s,1H,NH)
70	i-Bu	Ph	3365	1704	1715	10:3	0.88(d,J=7Hz,12H,CO₂CH,CH(CH₃)₂)‡; 1.9(m,2H,CO₂CH,CH(CH₃)₂)‡; 2.28(s,12H,=C-CH₃)‡; 3.62(s,6H,CO₂CH₃)‡; 3.86(m,4H,CO₂CH,CH(CH₃)₂)‡; 4.25(broad s,2H,[H-6']); 4.42(broad s,2H,H-4)‡; 4.46(broad s,2H,H-2'); 5.31(m,1H,H-5'); 5.56(m,1H,H-4'); 5.61(m,1H,[H-5']); 5.87(d,J=9.7Hz,1H,[H-4']); 6.4 and 6.6(two s,1H,[H-2']); 6.59 and 6.77(two d,J=7.8Hz,1H,H-6'); 7.1-7.7 (m,10H,NCO₂C₆H₅)‡; 8.89(s,1H,[NH]); 8.97(s,1H,NH)
71	i-Pr	t-Bu	3320	1704		4:1	1.2(two overlapping d,J=7Hz,12H,CO₂CH(CH₃)₂)‡; 1.43(s,18H,NCO₂C(CH₃)₃)‡; 2.24 and 2.26 (two s,6H,=C-CH₃)‡; 3.61(s,6H,CO₂CH₃)‡; 4.14(broad s,4H,H-2',[H-6']); 4.3(s,2H,H-4)‡; 4.9(m,2H,CO₂CH(CH₃)₂)‡; 5.16(m,1H,H-5'); 5.4-5.64(m,2H,H-4',[H-5']); 5.8(d,J=10.6Hz,1H,[H-4']); 6.34 and 6.52(two s,1H,[H-2']); 6.38 and 6.52 (two d, J=11Hz,1H,H-6'); 8.88(s,1H,[NH]); 8.96(s,1H,NH)

† H-n': refers to signals due to the 1',2'-dihydropyridyl isomer (a); [H-n']: refers to signals due to the 1',6'-dihydropyridyl isomer(b)
‡ Signals common to both 1',2'- and 1',6'-dihydropyridyl isomers
d Ratio determined from integration curves of NH and [NH] singlets
■ Assignments confirmed by double resonance experiments. All NH protons exchange with D₂O

TABLE XIV

Physical Properties of 3-Cyano-2,6-dimethyl-4-[3'(4')-(N-alkoxycarbonyl-1',2'-(1',6'-)dihydropyridyl)]1,4-dihydropyridines

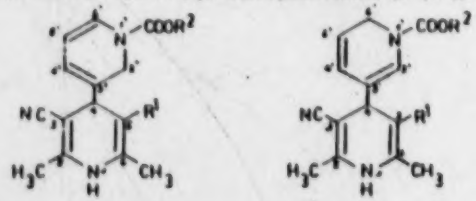


Comp.	R¹	R¹	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
72	CO_2Me	Me	125-127	73.4	$C_{17}H_{17}N_3O_4$	329	C=62.00 H=5.77 N=12.76	C=61.85 H=5.38 N=12.98
73	CO_2Me	Ph	131-132	62.1	$C_{23}H_{21}N_3O_4$	391	C=67.52 H=5.37 N=10.74	C=67.34 H=5.48 N=10.86
74	CN	Me	136-138	75.1	$C_{16}H_{16}N_4O_2$	296	C=64.86 H=5.40 N=18.92	C=64.71 H=5.34 N=19.24
75	CN	Ph	151-153	65.2	$C_{22}H_{16}N_4O_2$	358	C=70.39 H=5.03 N=15.64	C=70.46 H=5.24 N=15.94
76	CN	t-Bu	145-147	72.8	$C_{19}H_{22}N_4O_2$	338	C=67.45 H=6.51 N=16.57	C=67.72 H=6.37 N=16.71
77†	CN	Me	157-159	65.3	$C_{16}H_{16}N_4O_2$	296	C=64.86 H=5.40 N=18.92	C=64.91 H=5.74 N=19.21

† The 4-substituent is a 4'-(N-methoxycarbonyl-1',2'-dihydropyridyl) ring

TABLE XV

Spectroscopic Data for 3-Cyano-2,6-dimethyl-4-[3'(4')-[N-alkoxycarbonyl-1',2'-(1',6'-)dihydropyridyl]]1,4-dihydropyridines



(a) (b)

Comp.	R¹	R²	ir, cm⁻¹ (CHCl₃) NH	CN	NCO₂R²	Ratio§ a:b	¹H nmr, δ (DMSO-d₆)†‡
72	CO_2CH_3	Me	3352	2264	1688	5:3	2.0-2.18(two s,12H,=C-CH_3)‡; 3.76(s,6H,NCO_2CH_3)‡; 4.08(s,2H,H-4)‡; 4.2-4.4(m,4H,H-2',[H-6']); 5.32(m,1H,H-5'); 5.76(m,1H,[H-5']); 5.88(d,J=6Hz,1H,H-4'); 5.92(d,J=9.75Hz,1H,[H-4']); 6.8(s,1H,[H-2']); 6.72(d,J=7.4Hz,1H,H-6'); 9.49(s,1H,[NH]); 9.6(s,1H,NH)
73	CO_2CH_3	Ph	3352	2232	1704	11:9	2.0(s,12H,=C-CH_3)‡; 3.38(s,6H,CO_2CH_3)‡; 4.03-4.56(m,6H,H-2',[H-6'],H-4‡); 5.42(m,1H,H-5'); 5.8-6.02(m,3H,H-4',[H-4',H-5']); 6.68 and 6.94(two s,1H,[H-2']); 6.75 and 6.95(two d,J=7Hz,1H,H-6'); 7.23-7.6(m,10H,$NCO_2C_6H_5$)‡;9.5(s,1H,[NH]); 9.61(s,1H,NH)
74	CN	Me	3320	2220	1704	5:3	2.02,2.04(two s,12H,=C-CH_3)‡; 3.76(s,6H,NCO_2CH_3)‡; 4.07(s,2H,H-4)‡; 4.2-4.36(m,4H,H-2',[H-6']); 5.32(d,J=7.4Hz of d,J=6.2Hz,1H,H-5'); 5.77(m,1H,[H-5']); 5.86(m,J, ,=9.75Hz, 1H,[H-4']); 6.66(s,1H,[H-2']); 6.72(d,J=7.44Hz, 1H,H-6'); 9.47(s,1H,[NH]); 9.59(s,1H,NH)
75	CN	Ph	3332	2220	1720	7:3	2.0(s,12H,=C-CH_3)‡; 3.9-4.6(m,6H,H-2',[H-6'], H-4‡); 5.42(m,1H,H-5'); 5.63(m,1H,H-4'); 5.74-6.0(m,2H,[H-4',H-5']); 6.64(s,1H,[H-2']); 6.74(d,J=8.76Hz,1H,H-6'); 7.1-7.6(m,10H,$NCO_2C_6H_5$)‡; 9.32(s,1H,[NH]); 9.45(s,1H,NH)

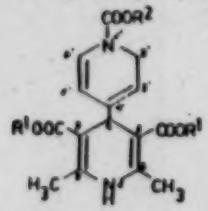
Table XV cont.

76	CN	t-Bu	3288	2220	1720	2:1	1.52 and 1.54(s,18H,$NCO_2C(CH_3)_3$)‡; 2.1 and 2.12(two s,12H,$=C-CH_3$)‡; 4.2-4.5(m,6H,H-2',[H-6'],H-4‡); 5.26(m,1H,H-5'); 5.78(m,1H,[H-5']); 5.86(d,J=6Hz,1H,H-4'); 5.92(d,J=9.75Hz,1H,[H-4']); 6.64(s,1H,[H-2']); 6.72(d,J=7Hz,H-6'); 9.52(s,1H,[NH]); 9.74(s,1H,NH)
77i	CN	Me	3288	2192	1720	d	2.0(s,6H,$=C-CH_3$); 3.76(s,3H,NCO_2CH_3); 3.92(s,1H,H-4); 4.34(s,2H,H-2'); 5.24(d,J=8.64Hz,1H,H-5'); 5.45(broad s,1H,H-3'); 6.86(d,J=8.64Hz,1H,H-6'); 9.52(s,1H,NH)

i The 4-substituent is a 4'-(N-methoxycarbonyl-1',2'-dihydropyridyl) group
† H-n': refers to signals due to the 1',2'-dihydropyridyl isomer(a); [H-n']: refers to signals due to the 1',6'-dihydropyridyl isomer (b)
‡ Signals common to both 1',2'- and 1',6'-dihydropyridyl isomers
d Ratio determined from integration curves of NH and [NH] singlets
■ Assignments confirmed by double resonance experiments. All NH protons exchange with D_2O

TABLE XVI

Physical Properties of Dialkyl 2,6-dimethyl-4-{4'-(N-alkoxycarbonyl-1',2'-dihydropyridyl)}-1,4-dihydropyridine-3,5-dicarboxylates



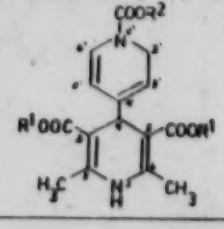
Comp.	R^1	R^2	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
78	Me	Me	182-184	73.8	$C_{19}H_{22}N_2O_8$	362	C=59.67 H=6.07 N=7.73	C=59.24 H=6.26 N=7.58
79	Et	Me	145-148	75.6	$C_{20}H_{24}N_2O_8$	390	C=61.54 H=6.66 N=7.18	C=61.41 H=6.77 N=7.30
80	i-Bu	Me	161-163	78.6	$C_{23}H_{30}N_2O_8$	446	C=64.57 H=7.62 N=6.28	C=64.32 H=7.81 N=6.56
81	Me	Ph	159-161	65.2	$C_{23}H_{20}N_2O_8$	424	C=65.09 H=5.66 N=6.60	C=64.92 H=5.41 N=6.43
82	Et	Ph	128-129	61.2	$C_{24}H_{24}N_2O_8$	452	C=66.37 H=6.19 N=6.19	C=66.71 H=6.32 N=6.32
83	i-Bu	Ph	167-169	62.6	$C_{27}H_{32}N_2O_8$	508	C=68.50 H=7.08 N=5.51	C=68.36 H=7.17 N=5.62
84	Et	t-Bu	165-167	67.2	$C_{24}H_{28}N_2O_8$	432	C=63.89 H=7.41 N=6.48	C=63.58 H=7.32 N=6.71

Table XVI cont.

85	i-Bu	t-Bu	126-128	73.1	$C_{21}H_{28}N_2O_4$	488	C=66.39 H=8.19 N=5.74	C=66.48 H=8.38 N=5.51

TABLE XVII

Spectroscopic Data for Dialkyl 2,6-dimethyl-4-[4'-(N-alkoxycarbonyl-1',2'-dihydropyridyl)]-1,4-dihydropyridine-3,5-dicarboxylates



Comp.	R¹	R²	ir,cm⁻¹(CHCl₃) NH	CO₂R²	NCO₂R²	¹H nmr,δ (CDCl₃)
78	Me	Me	3310	1710		2.24(s,6H,=C-CH₃); 3.6(s,6H,CO₂CH₃); 3.66(s,3H,NCO₂CH₃); 4.18(broad s,2H,H-2'); 4.38(s,1H,H-4); 5.05(m,1H,H-3'); 5.12(m,1H,H-5'); 6.62(d,J=7Hz,1H,H-6'); 8.92(s,1H,NH)‡■
79	Et	Me	3340	1695	1705	1.22(t,J=7Hz,6H,CO₂CH₂CH₃); 2.26(s,6H,=C-CH₃); 3.7(s,3H,NCO₂CH₃); 4.12(two overlapping q, 4H,CO₂CH₂CH₃); 4.2(d,J=2.5Hz,2H,H-2'); 4.41(s,1H,H-4); 5.12-5.24(m,2H,H-3',H-5'); 6.65(d,J=7.5Hz,1H,H-6'); 8.82(s,1H,NH)‡ ■
80	i-Bu	Me	3352	1688-1704		1.06(d,J=6Hz,12H,CO₂CH₂CH(CH₃)₂); 2.06(m,2H,CO₂CH₂CH(CH₃)₂); 2.4(s,6H,=C-CH₃); 3.8(s,3H,NCO₂CH₃); 4.03(d,J=6Hz,4H,CO₂CH₂CH(CH₃)₂); 4.23(s,1H,H-4); 4.33(m,2H,H-2'); 5.36(m,2H,H-4',H-5'); 6.6(m,1H,H-6'); 7.23(s,1H,NH)‡
81	Me	Ph	3360	1702	1715	2.33(s,6H,=C-CH₃); 3.76(s,6H,CO₂CH₃); 4.4(m,2H,H-2'); 4.55(s,1H,H-4); 5.16-5.43(m,2H,H-3', H-5'); 6.1(s,1H,NH); 6.83(m,1H,H-6'); 7.0-7.5(m,5H,NCO₂C₆H₅)
82	Et	Ph	3380	1702	1720	1.33(t,J=6Hz,6H,CO₂CH₂CH₃); 2.33(s,6H,=C-CH₃); 4.2(q,J=6Hz,4H,CO₂CH₂CH₃); 4.4(m,2H,H-2'); 4.58(s,1H,H-4); 5.2-5.53 (m,2H,H-3',H-5'); 5.86(s,1H,NH)‡; 6.6-6.96(m,1H,H-6'); 7.0-7.66(m,5H,NCO₂C₆H₅);
83	i-Bu	Ph	3368	1688-1720		0.93(d,J=7Hz,12H,CO₂CH₂CH(CH₃)₂); 1.92(m,2H,CO₂CH₂CH(CH₃)₂); 2.3(s,6H,&MG>); 3.88(m,4H,CO₂CH₂CH(CH₃)₂); 4.28 and 4.48(two broad s,2H,H-2'); 4.56(s,1H,H-4); 5.22(broad s,1H,H-3'); 5.32(d,J, . =8.62Hz,H-5'); 6.69 and 6.88(two d,J=8.62Hz,1H,H-6'); 8.92(s,1H,NH)■
84	Et	t-Bu	3352	1704		1.3(t,J=7Hz,6H,CO₂CH₂CH₃); 1.4(s,9H,NCO₂C(CH₃)₃); 2.3(s,6H,=C-CH₃); 3.96-4.46(m,7H,H-2',H-4, CO₂CH₂CH₃); 5.0-5.36(m,2H,H-3',H-5'); 6.33(s,1H,NH)‡; 6.63(d,J=8Hz,1H,H-6')

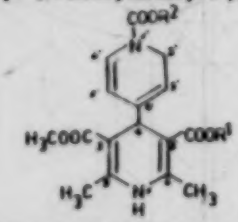
Table XVII cont.

85	i-Bu	t-Bu	3370	1704	1.0(d,J=6Hz,12H,$CO_2CH_2CH(CH_3)_2$); 1.3(s,9H,$NCO_2C(CH_3)_3$); 2.0(m,2H,$CO_2CH_2CH(CH_3)_2$); 2.4(s,6H,$=C-CH_3$); 4.0(d,J=6Hz,2H,$CO_2CH_2CH(CH_3)_2$); 4.35(d,J=5Hz,2H,H-2'); 4.6(s,1H,H-4); 5.1-5.5(m,2H,H-3',H-5'); 6.5(m,2H,H-6',NH‡)

‡ Exchanges with D_2O
■ Spectrum run in DMSO-d_6

TABLE XVIII

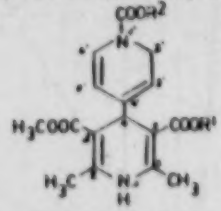
Physical Properties of 3-Alkyl-5-methyl-2,6-dimethyl-4-[4'-(N-alkoxycarbonyl-1',2'-dihydropyridyl)]-1,4-dihydropyridine-3,5-dicarboxylates



Comp.	R¹	R'†	mp°C	% Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
86	i-Bu	Me	171-173	78.6	$C_{31}H_{44}N_2O_6$	404	C=62.37 H=6.93 N=6.93	C=62.47 H=7.15 N=7.22
87	i-Bu	Ph	168-169	67.2	$C_{36}H_{46}N_2O_6$	466	C=66.95 H=6.44 N=6.01	C=67.16 H=6.76 N=6.22
88	i-Pr	t-Bu	173-175	70.3	$C_{31}H_{44}N_2O_6$	432	C=63.89 H=7.41 N=6.48	C=63.91 H=7.38 N=6.56
89	i-Bu	t-Bu	148-149	73.4	$C_{33}H_{46}N_2O_6$	446	C=64.57 H=7.62 N=6.28	C=64.72 H=7.44 N=6.36

TABLE XIX

Spectroscopic Data for 3-Alkyl-5-methyl-2,6-dimethyl-4-[4'-(N-alkoxycarbonyl-1',2'-dihydropyridyl)]-1,4-dihydropyridine-3,5-dicarboxylates

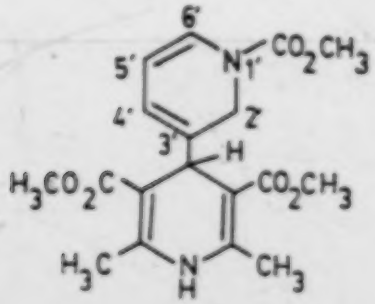


Comp.	R¹	R²	ir, cm⁻¹ (CHCl₃) NH	CO₂R¹	NCO₂R²	¹H nmr, δ (CDCl₃)
86	i-Bu	Me	3336	--1690--		0.96(d, J = 7Hz, 6H, $CO_2CH_2CH(CH_3)_2$); 2.0(m, 1H, $CO_2CH_2CH(CH_3)_2$); 2.32 and 2.34(two s, 6H, =C-CH_3); 3.74(s, 3H, CO_2CH_3); 3.78(s, 3H, NCO_2CH_3); 3.90(m, 2H, $CO_2CH_2CH(CH_3)_2$); 4.32(broad s, 2H, H-2'); 4.55(s, 1H, H-4); 5.22(m, 2H, H-3', H-5'); 6.25(s, 1H, NH)‡; 6.62 and 6.73 (two d, J = 7.6Hz, 1H, H-6')
87	i-Bu	Ph	3320	1688	1704	0.97(d, J = 7Hz, 6H, $CO_2CH_2CH(CH_3)_2$); 2.0(m, 1H, $CO_2CH_2CH(CH_3)_2$); 2.26 and 2.27(two s, 6H, =C-CH_3); 3.73(s, 3H, CO_2CH_3); 3.94(m, 2H, $CO_2CH_2CH(CH_3)_2$); 4.37 and 4.52(two d, J = 3.43Hz, 2H, H-2'); 4.57(s, 1H, H-4); 5.24(broad s, 1H, H-3'); 5.32(d, J = 8.02Hz, 1H, H-5'); 6.37(s, 1H, NH)‡; 6.73 and 6.82(two d, J = 8.02Hz, 1H, H-6'); 7.06-7.5(m, 5H, $NCO_2C_6H_5$)
88	i-Pr	t-Bu	3336	1688		1.3(two overlapping d, J = 7Hz, 6H, $CO_2CH(CH_3)_2$); 1.52(s, 9H, $NCO_2C(CH_3)_3$); 2.36 and 2.40(two s, 6H, =C-CH_3); 3.78(s, 3H, CO_2CH_3); 4.32(d, J = 4.89Hz, 2H, H-2'); 4.53(s, 1H, H-4); 4.96-5.3(m, 3H, $CO_2CH(CH_3)_2$, H-3', H-5'); 6.63 and 6.74(two d, J = 7.68Hz, 1H, H-6'); 6.8(s, 1H, NH)‡
89	i-Bu	t-Bu	3368	1676		0.98(d, J = 6.7Hz, 6H, $CO_2CH_2CH(CH_3)_2$); 1.5(s, 9H, $NCO_2C(CH_3)_3$); 2.0(m, 1H, $CO_2CH_2CH(CH_3)_2$); 2.32 and 2.34(two s, 6H, =C-CH_3); 3.74(s, 3H, CO_2CH_3); 3.9(d, J = 7Hz, 2H, $CO_2CH_2CH(CH_3)_2$); 4.27(d, J = 3.85Hz, 2H, H-2'); 4.54(s, 1H, H-4); 5.16(m, 2H, H-3', H-5'); 6.6(d, J = 10.5Hz, 1H, H-6'); 8.45(s, 1H, NH)‡

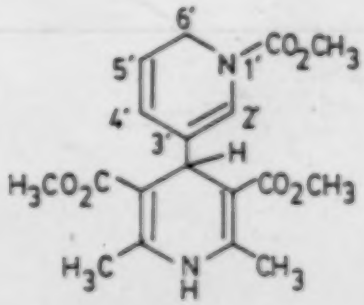
‡ Exchanges with D_2O

The ^1H nmr spectrum of analogues possessing a [3'-[N-alkoxycarbonyl-1',2'-(1',6'-)dihydropyridyl]] substituent attached to the 4-position of the 1,4-dihydropyridine ring can be interpreted in the same way as compound 58 which is described in detail below.

The ^1H nmr spectrum of 58 indicated that the product was a mixture of two isomers; one isomer having a 4-[3'-(1',2'-dihydropyridyl)] substituent (58a) and the other, a 4-[3'-(1',6'-dihydropyridyl)] ring substituent (58b).



58a



58b

The ^1H nmr spectrum for 58a and 58b (δ 4-7) is shown in Figure 4a. The spectrum exhibited eight different resonance signals for the protons present in the 1',2'- and 1',6'-dihydropyridine ring. The singlet at δ 4.36 was due to H-4.

Double irradiation experiments allowed assignment of each resonance signal to a specific proton in the 1',2'-(1',6'-)dihydropyridine ring. Figure 4b shows those protons which couple to each other in the ^1H nmr spectrum. The double resonance experiments indicated that the signals at δ6.56, 5.52, 5.22 and 4.2 (signals labelled as a,e,f and h respectively) are associated with one isomer ("Isomer I"), whereas the peaks at δ 6.36, 5.8, 5.56 and 4.16 (b,c,d and i respectively) are the resonance frequencies for the protons attached to the other isomer ("Isomer II"). These assignments were consistent with the integration curve for the resonance signals. Integration also showed that the ratio "Isomer I": "Isomer II" was 9:7 (Fig. 4a).

Analysis of the resonance signals due to protons of "Isomer I".

	∂		∂		∂
a:	6.56	d:	5.56	g:	4.36
b:	6.36	e:	5.52	h:	4.2
c:	5.8	f:	5.22	i:	4.16

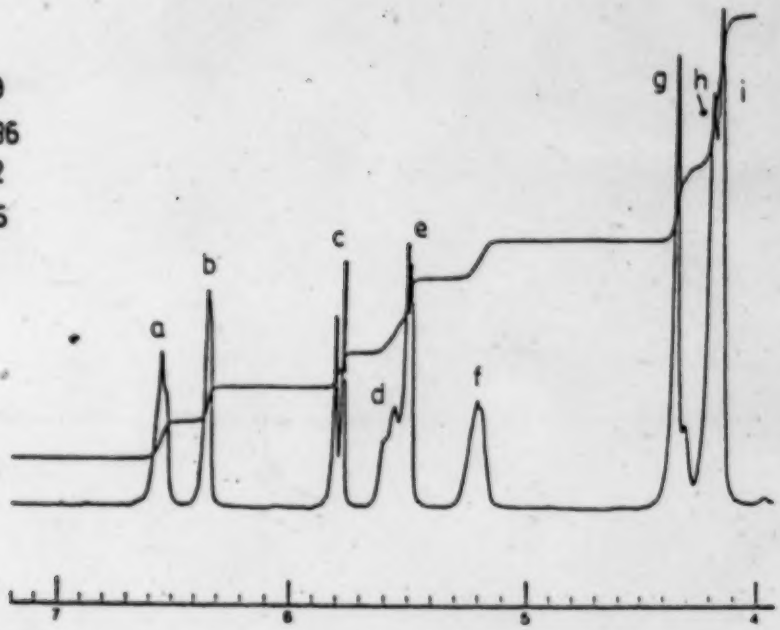


Fig. 4a 300 MHz ^1H nmr spectrum (DMSO-d_6) for 58 (∂ 4-7).

Isomer I (58a):

Isomer II (58b):

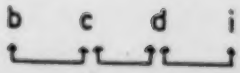
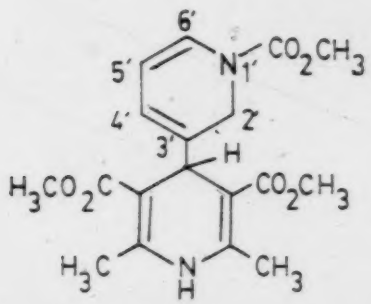


Fig. 4b ^1H nmr signals assigned to each isomer present in 58. The arrows indicate which protons couple to each other.

The doublet at δ6.56 (a, J=6.1Hz) can be assigned to the most deshielded hydrogen present in the 1',2'- (or 1',6'-) dihydropyridine ring since it is a vinylic proton vicinal to nitrogen. The signal at δ 4.2 (h) is due to two protons also vicinal to nitrogen. These protons are shielded relative to (a) because they are attached to a sp^3 hybridized carbon atom. The two multiplets at δ 5.52 (e) and 5.22 (f) appear in the olefinic range suggesting (e) and (f) are vinylic protons.

It is known that hydrogens attached to the 4-position of a 1,2-dihydropyridyl ring are deshielded relative to protons attached to the 3-(5-)position of the 1,2-(1,6-)dihydropyridyl ring[172]. Hence, proton (e) must be assigned to H-4' and (f) to H-5'. The resonance signal for H-5' showed strong coupling to the vinylic proton vicinal to nitrogen (a, 6.56δ). This indicated that those two hydrogens (a and f) are attached to adjacent carbon atoms. The 1',2'-dihydropyridyl isomer 58a is consistent with these ^1H nmr spectroscopic data whereas 58b is not. The final chemical shift assignment for the protons present in 58a is shown below.



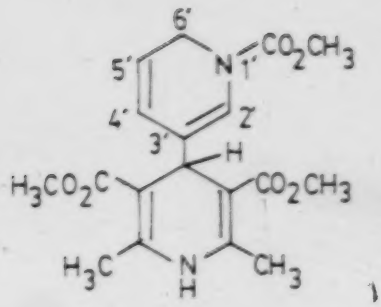
58a

	δ
H-6'	6.56
H-5'	5.22
H-4'	5.52
H-2'	4.2

Analysis of the ^1H nmr signals due to "Isomer II".

"Isomer II" has been assigned to structure 58b which has a [3'-(1,6'-dihydropyridyl)] substituent atached to the 4-position of the 1,4-dihydropyridyl ring. The group of chemical shifts attributed to this isomer include:

The assignment of "Isomer II" to compound 58b is in agreement with the observation that the vinylic proton vicinal to nitrogen (H-2') appeared as a broad singlet which sharpened



58b

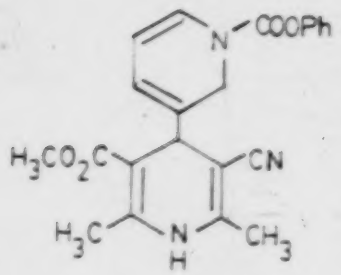
	δ
H-6'	4.16
H-5'	5.56
H-4'	5.8
H-2'	6.36

upon irradiation of resonance (c) at 5.8δ. This indicated that H-2' undergoes a small four-bond coupling to H-4'. This structural assignment is also consistent with the fact that the protons at 4.16δ (H-6') coupled to H-5'.

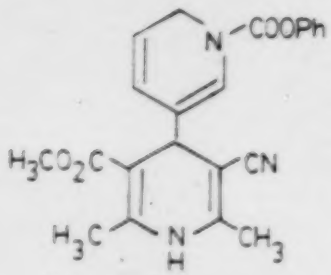
The ^{1}H nmr spectra for derivatives possessing a {3'-[N-phenoxycarbonyl-1',2'-(1',6'-)dihydropyridyl]} substituent attached to the 4-position of the 1,4-dihydropyridyl ring (62-65,70,73,75) were similar to that obtained for 58 but they were more complex. The spectral interpretation for methyl 3-cyano-2,6-dimethyl-4-{3'-[N-phenoxycarbonyl-1',2'-(1',6'-)dihydropyridyl]}-1,4-dihydropyridine-5-carboxylate 73 is explained below.

The ^{1}H nmr spectrum for 73 displaying the range from δ 4.3 to 7.0 is shown in Figure 5a. This portion of the ^{1}H nmr spectrum shows the resonances assigned to the protons in the 1',2'- and 1',6'-dihydropyridyl ring. The spectrum exhibited two doublets at δ6.94 and 6.75 (J=7.5Hz) and two singlets at δ6.94 and 6.68. These four resonances integrated for two hydrogens which were assigned to the vinylic protons vicinal to nitrogen. The remaining vinylic protons (H-4', H-5') appeared as three multiplets at δ 6.02-5.9 and 5.86, which integrated for

three hydrogens, and another multiplet at δ 5.42 which integrated for one hydrogen. The methylene protons of the 1',2'- and 1',6'-dihydropyridine ring appeared as four broad singlets at δ 4.58, 4.52, 4.36 and 4.3. The four singlets integrated for four hydrogens. The spectrum also showed a singlet at δ 4.1 and a doublet at δ 4.0 (J = 2.5Hz) which were assigned to H-4.



73a



73b

Double irradiation experiments indicated that the signals at δ 6.94, 6.75, 5.86, 5.42, 4.52 and 4.3 were due to protons present in the same isomer. This isomer was assigned to the 4-[3'-(1',2'-dihydropyridyl)] isomer 73a following the same rationale used to interpret the ^{1}H nmr spectrum of 58 (*vide supra*).

Double resonance experiments also indicated that the signals at δ 6.92, 6.68, 6.02-5.9, 4.58 and 4.36 were due to the protons in a single isomer. This compound was assigned structure 73b which is the 4-[3'-(1',6'-dihydropyridyl)] isomer. The same rationale used to distinguish 1',2'-and 1',6'-dihydropyridyl isomers for compound 58 was utilized for the assignment of 73b (*vide supra*).

The ^{1}H nmr spectrum showed two doublets (δ 6.94 and 6.75) for H-6' and two singlets (δ 6.92 and 6.68) for H-2' in 73a. The three protons vicinal to nitrogen in 73b also exhibited dual absorptions. These dual absorptions for the hydrogens vicinal to nitrogen in 73 may be due to the presence of two rotamers with different configurations about the nitrogen-to-carbonyl bond. The difference in configuration is likely due to restricted rotation about the N-CO bond, owing to its double bond character, as illustrated below.

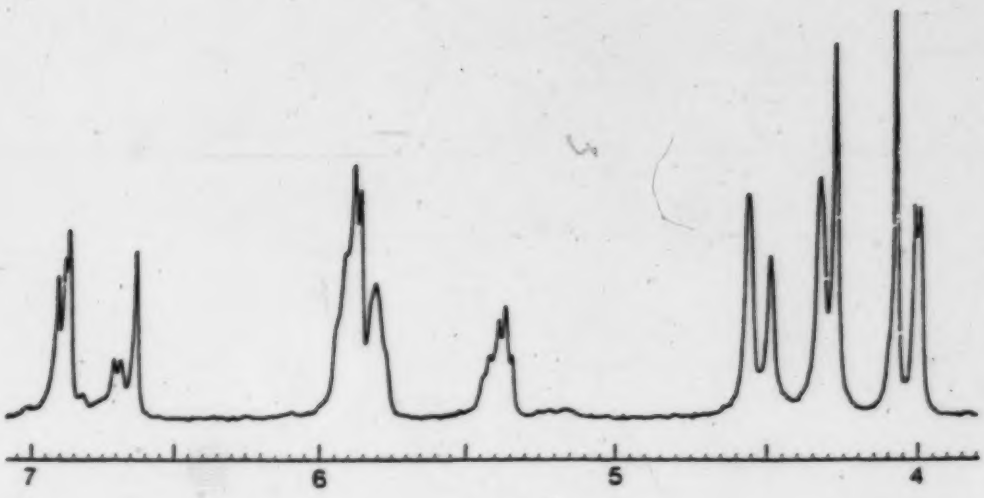


Fig. 5a 300 MHz ^1H nmr spectrum (DMSO-d_6) of 73 at 25°C (∂ 4-7)

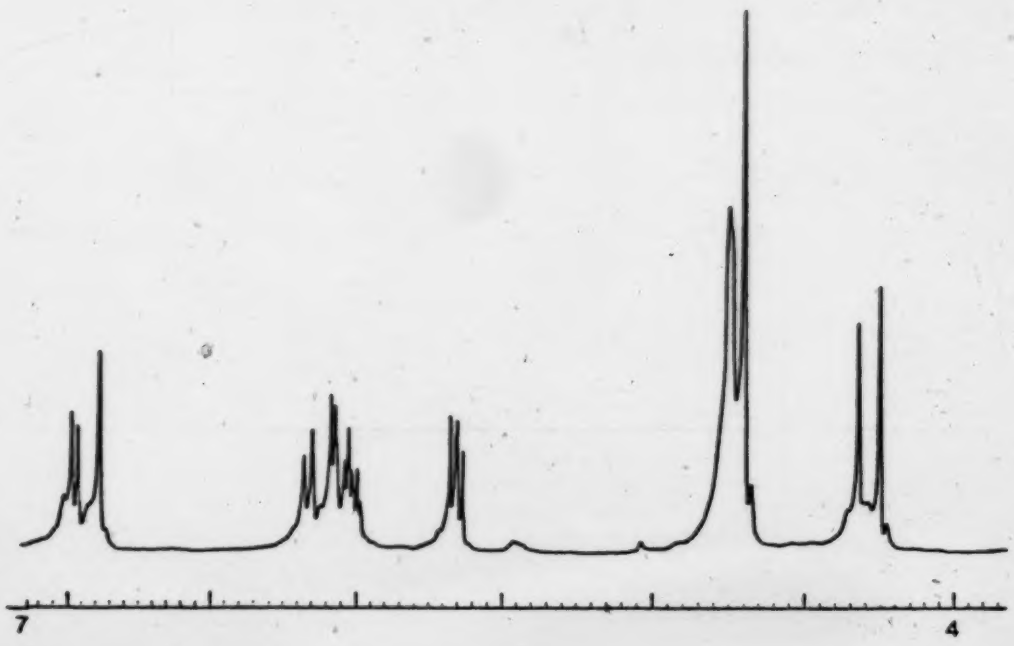
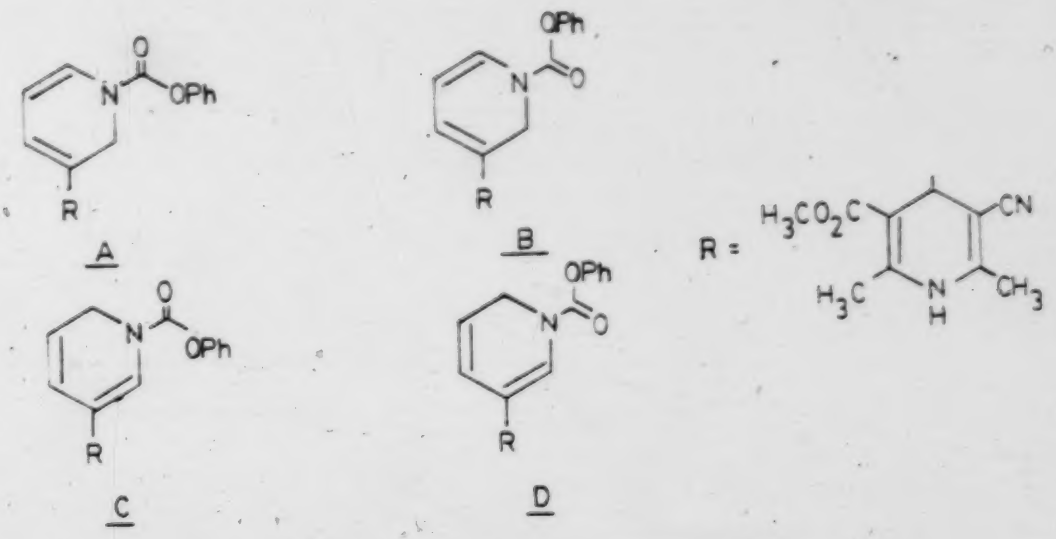


Fig. 5b 300 MHz ^1H nmr spectrum (DMSO-d_6) of 73 at 115°C (∂ 4-7)

Thus, each of the isomers 73a and 73b exist in two different rotameric configurations A, B and C,D respectively.



The ^{1}H nmr spectrum of 73 determined at 115°C (DMSO-d_6) is shown in Figure 5b. The effect of increased temperature (115°C) upon the ^{1}H nmr spectrum is summarized below.

i) The two doublets at δ 6.94 and 6.75 (H-6', 1',2'-dihydropyridyl isomer) underwent near complete coalescence to one doublet at δ 6.85.

ii) The two singlets at δ 6.92 and and 6.68 (H-2', 1',6'-dihydropyridyl isomer) coalesced into one singlet at δ 6.75.

iii) The two broad singlets at δ 4.58 and 4.36 (H-6', 1',6'-dihydropyridyl isomer) became a broad singlet at δ 4.45.

iv) The two singlets at δ 4.52 and 4.3 (H-2', 1',2'-dihydropyridyl isomer) coalesced to a sharp singlet at δ 4.4.

These results confirmed the presence of two rotamers for each 74a and 74b. Increasing the temperature to 115° lowered the energy barrier for rotation about the N-CO bonds. Thus, the two dual absorptions observed for a particular hydrogen coalesced to give a single resonance representative of the average chemical shifts for the populations of both rotamers.

The presence of rotamers was observed only for those derivatives possessing a N-phenoxycarbonyl substituent at the 1'-position of the 1',2'-(1',6'-)dihydropyridyl ring. It appeared that the phenoxy substituent of the carbamate moiety confers a greater double-bond character to the N-CO bond than a methoxy or t-butoxy group for this class of nifedipine analogues. The presence of rotamers may be due to the electron-withdrawing effect of the phenyl group since rotamers were not observed for compounds having an electron-donating methyl or t-butyl substituent.

The ratio 1',2'-:1',6'-dihydropyridyl isomer was determined from the integration curve of the ^{1}H nmr spectrum of the mixture. The resonance signals used to calculate the isomeric ratios were the two different NH singlets or the H-2' (1',6'-isomer) and H-6' (1',2'-isomer) peaks which were well resolved. In all reactions the 1',2'-dihydropyridyl isomer was the predominant product. Steric effects due to the 1,4-dihydropyridine ring are expected to be greatest at C-2', which would result in preferential formation of the 1',6'-dihydropyridyl isomer. Since this was not the case, factors other than steric effects of the 1,4-dihydropyridyl ring must be significant. The oxygen atoms of the carbonyl groups in the C-3 and/or C-5

substituents attached to the 1,4-dihydropyridine ring may adopt an orientation such that the lone-electron pairs (and/or the π-electrons of the carbonyl group itself) may interact with sodium borohydride directing attack to the C-2' position which is in closer proximity than the C-6' position. This would explain, at least in part, the selective formation of the 1',2'-dihydropyridyl isomer which was the predominant product in all reactions.

Pharmacological Evaluation of Dialkyl 2,6-dimethyl-4-{3'-(4'-)[N-alkoxycarbonyl-1',2'-(1',6'-)-dihydropyridyl]}-1,4-dihydropyridine-3,5-dicarboxylates and 3-Cyano-2,6-dimethyl-4-{3'-(4'-)[N-alkoxycarbonyl-1',2'-(1',6'-)dihydropyridyl]}-1,4-dihydropyridines

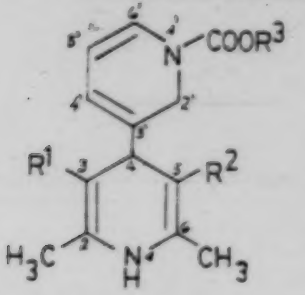
A number of selected 4-{3'(4')-[N-alkoxycarbonyl-1',2'-(1',6'-)dihydropyridyl]}-1,4-dihydropyridines were tested as calcium channel blockers. The pharmacological test procedure was identical to that described previously for the 4-pyridyl-1,4-dihydropyridines The ID_{10} values obtained for compounds 58, 59, 69, 70, 73, 75, 78, 84, 88 and 89 are presented in Table XX.

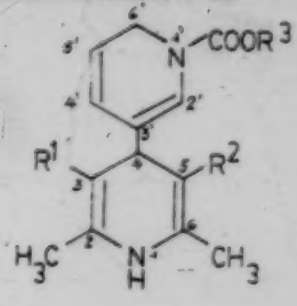
Compounds having a 4-{3'-[N-alkoxycarbonyl-1',2'(1',6')-dihydropyridyl]} substituent (58,59,69,70,73,75) will be discussed first.

Reduction of the 4-(3'-pyridyl) moiety to a 1',2'(1',6')-dihydropyridyl ring and the concomintant introduction of the N-alkoxycarbonyl substituent resulted in increased pharmacological activity. Activity was enhanced approximately 10-fold relative to the parent pyridine. The stereochemical features of 4-[1',2'(1',6')-dihydropyridyl]-1,4-dihydropyridines may influence their pharmacological activity. The 1',2'(1',6')-dihydropyridyl ring may be approximately perpendicular to the 1,4-dihydropyridine. The N-alkoxycarbonyl substituent may force the 1,4-dihydropyridine to adopt a more planar conformation to minimize the non-bonded interactions between the C-3, C-4 and C-5 substituents. In addition, the 1',2'(1',6')-dihydropyridyl moiety is almost planar and has a relatively high degree of unsaturation. Hence, the conformation of these 4-(dihydropyridyl)-1,4-dihydropyridines may

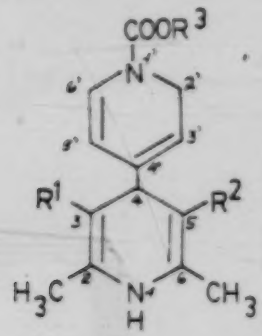
TABLE XX

Inhibitory activities of 2,6-dimethyl-4-[3'(4')-(N-alkoxycarbonyl-1',2'(1',6')dihydropyridyl)]-1,4-dihydropyridines on contractile responses to CD





Comp.	R^1	R^2	R^3	ID_{50} (M)
58	CO_2Me	CO_2Me	Me	2.5×10^{-7} (2)
59	CO_2Et	CO_2Et	Me	$(1.8\pm0.5)\times10^{-7}$ (3)
69	CO_2Me	CO_2iBu	Me	$(3.3\pm1.0)\times10^{-8}$ (4)
70	CO_2Me	CO_2iBu	Ph	$(4.5\pm1.5)\times10^{-8}$ (3)
72	CO_2Me	CN	Me	$(6.4\pm0.6)\times10^{-5}$ (2)
74	CN	CN	Me	$(3.3\pm0.5)\times10^{-5}$ (2)



77	CN	CN	Me	$(3.6\pm0.5)\times10^{-5}$ (2)
83	CO_2iBu	CO_2iBu	Ph	$(5.1\pm1.6)\times10^{-7}$ (3)
86	CO_2Me	CO_2iBu	Me	$(1.7\pm0.4)\times10^{-6}$ (4)
87	CO_2Me	CO_2iBu	Ph	$(8.1\pm3.5)\times10^{-5}$ (3)

† $ID_{50}\pm$SD. No. of experiments in parentheses.

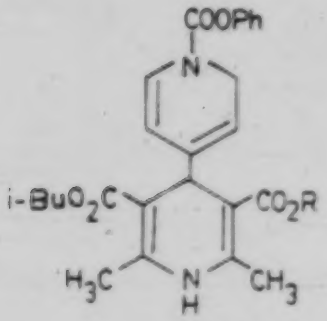
be very similar to that of nifedipine analogues which have a 4-(meta-substituted phenyl) group. This would explain why they are more active than the 4-pyridyl precursors which have been considered similar to nifedipine derivatives having a 4-unsubstituted-phenyl moiety.

The 1,4-dihydropyridine C-3 and C-5 substituents influenced activity in a manner analogous to that described for the 4-pyridyl analogues. Thus, compound 58,having a C-3 and C-5 methoxycarbonyl substituents, was less active than 59 which possesses C-3 and C-5 ethoxycarbonyl substituents. The presence of a 3-CN group caused a marked reduction in activity. Compounds having two different C-3 and C-5 substituents (69,70) exhibited increased potency (ID_{50} 10^{-8} M) relative to those having identical C-3 and C-5 substituents.

Compounds 69 and 70 have C-3 methoxycarbonyl and C-5 i-butoxycarbonyl substituents.They have different N-alkoxycarbonyl groups present in the 1',2'-(1',6'-)dihydropyridyl ring. The derivative 69 has a N-methoxycarbonyl substituent whereas 70 has a N-phenoxycarbonyl group.The analogue 69 was slightly more potent than 70. It appears that neither the size nor the aromatic (aliphatic) character of the N-substituent is crucial to the calcium antagonistic activity of these nifedipine analogues. However this observation is based on only two compounds and by no means can be generalized. It should also be pointed out that the 4-(3'-dihydropyridyl)-1,4-dihydropyridines tested within this group were mixtures of 1',2'- and 1',6'-dihydropyridyl isomers. Therefore the ID_{50} values obtained only indicated the activity of such mixtures. If the 1',2'-isomers are equiactive with the 1',6'-isomers, then the ID_{50} values observed may reflect their true pharmacological activity. However, if one isomer is substantially more active than the other, the ID_{50} values will be misleading. The more potent isomer may have an ID_{50} considerably lower than that obtained for the mixture. Therefore, the pharmacological results just discussed are to be treated cautiously and considered as approximations.

The 4-[4'-(N-alkoxycarbonyl-1',2'-dihydropyridyl)]-1,4-dihydropyridines were less active than the corresponding 4-{3'-[N-alkoxycarbonyl-1',2'-(1',6'-)dihydropyriyl]}

analogues. The 3-isopropyl 5-methyl 2,6-dimethyl-4-[4'-(N-phenoxycarbonyl-1',2'-dihydropyridyl)]-1,4-dihydropyridine-3,5-dicarboxylate 88 exhibited a 100-fold decrease in pharmacological activity (ID_{50}=1.7 X 10^{-6} M) relative to the 4-(3'-dihydropyridyl) analogue 70 (ID_{50}=4.5 X 10^{-9} M). Once again, the presence of a 3-CN substituent, as in 78, is detrimental to activity (ID_{50}=3.6 X 10^{-9} M).



83: R=i-Bu
87: R=Me

The analogue 84, having identical C-3 and C-5 i-butoxycarbonyl substituents exhibited an ID_{50} of 5.1 X 10^{-7} M. In contrast, compound 89, which has a C-3 i-butoxycarbonyl and a C-5 methoxycarbonyl substituents, was 100-fold less active than 84. The significance of this aberration in the ID_{50} values of these calcium antagonists is uncertain.

In contrast to the 4-(3'-[1',2'(1',6')-dihydropyridyl]) analogues, the 4-[4'-(1',2'-dihydropyridyl)]-1,4-dihydropyridines were generally less active than the corresponding parent 4-(4'-pyridyl) derivatives.

Introducing a N-substituent into the 1'-position of the 4-[4'-(1',2'-dihydropyridyl)]-1,4-dihydropyridine may be regarded as similar to the introduction of a substituent at the para position of the C-4 phenyl ring in other nifedipine analogues. As previously mentioned, such a substituent may not significantly affect the overall conformation of the molecule. The 1,4-dihydropyridine ring may tend to pucker to alleviate interactions between the C-3, C-4 and C-5 substituents. Thus, the activity of such a compound

might be expected to be similar to the corresponding unsubstituted analogue. Nevertheless, reduction of the 4-pyridinyl substituent introduced other changes in the molecule such as:

(i) Planarity of the 4-substituent is lost. The 1',2'-dihydropyridyl ring has two sp^3 atoms which will cause ring puckering.

(ii) The π-electron density decreases upon saturation of a double bond.

(iii) Aromaticity is lost, as a consequence of (i) and (ii).

These changes may in part cause the observed reduction in calcium antagonistic activity. The conformational and electronic characteristics of the 4-substituent present in the 1,4-dihydropyridine ring may also be significant for the calcium antagonistic effects of nifedipine analogues.

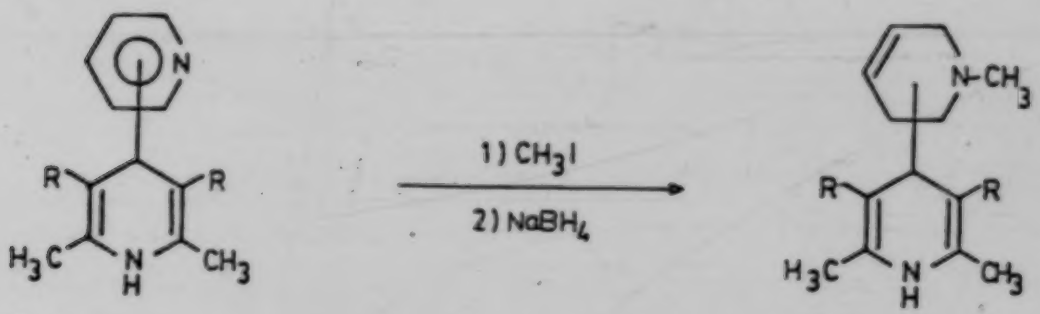
C. *Compounds Having a N-methyl-1',2',3',6'-tetrahydropyridyl Substituent at C-4*

Dialkyl 2,6-dimethyl-4-{2'-(4'-,5'-)[N-methyl-1',2',3',6'-tetrahydropyridyl]}-1,4-dihydropyridine-3,5-dicarboxylates (92-97)

The derivatives 92-97 have a 1',2',3',6'-tetrahydropyridyl ring attached to the 4-position of the 1,4-dihydropyridine ring. These compounds were prepared by the sodium borohydride reduction of the methyl iodide salts of compounds 30,34,38,42,46 and 50 (Scheme XII). A typical synthetic procedure is described below for the synthesis of 92.

Dimethyl 2,6-dimethyl-4-(2'-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (0.01 mol) was dissolved in acetone (50 mL). Iodomethane (0.03 mol) was added and the mixture was heated under reflux for 9 h. The resulting suspension was allowed to cool to room temperature and the solvent was removed *in vacuo* . The resulting pyridinium iodide was dissolved in 20 mL of aqueous ethanol (1:1 v/v) and cooled to 0°C. This solution was added

dropwise to a solution of sodium borohydride (0.05 mol) in absolute ethanol precooled to 0°C. The reaction mixture was stirred at 0°C for 5 h. Water (50 mL)was added at which time the product separated as a solid. The crude 4-(tetrahydropyridyl)-1,4-dihydropyridine was filtered and recrystallized from aqueous ethanol. Some of the physical data for the products synthesized are illustrated in Table XXII. The pyridinium iodides were obtained in quantitative yield. Alkylation of the 1,4-dihydropyridine nitrogen did not occur, indicating that the pyridine nitrogen is a stronger nucleophile than the 1,4-dihydropyridine nitrogen. The 1,4-dihydropyridine nitrogen is likely deactivated towards reaction with electrophiles due to the double enamine system and the electron-withdrawing effects of the conjugated ester groups at C-3 and C-5.



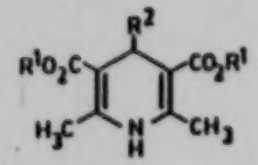
R=COOMe, COOEt

SCHEME XII

The sodium borohydride reduction of of 4-(3'-pyridyl)-1,4-dihydropyridine methiodide salts afforded exclusively one of two possible isomers namely, dialkyl 2,6-dimethyl-4-[5'-(N-methyl-1',2',3',6'-tetrahydropyridyl)]-1,4-dihydropyridine-3,5-dicarboxylates of general structure III. The ^{1}H nmr spectroscopic data were consistent with the structure assigned (*vide infra*). The course of the reduction may depend upon the relative stability of the products. Compounds 96 and 97 are probably favored as they possess a more highly substituted double bond. The other possible product, of general structure IV, possesses a

TABLE XXI

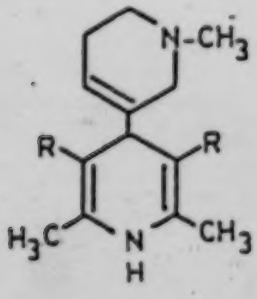
Physical Properties of Dialkyl 2,6-dimethyl-4-[2'-(4-',5'-)[N-methyl-1',2',3',6'-tetrahydropyridyl]]-1,4-dihydropyridine-3,5-dicarboxylates



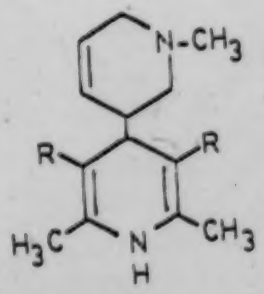
Comp.	R^1	R'†	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
90	Me	2'- thp	159-161	77.8	$C_{17}H_{20}N_2O_4$	320	C=63.75 H=7.50 N=8.75	C=63.42 H=7.36 N=9.06
91	Et	2'- thp	131-133	75.6	$C_{19}H_{24}N_2O_4$	348	C=65.52 H=8.05 N=8.05	C=65.63 H=7.87 N=7.92
92	Me	4'- thp	133-134	92.1	$C_{17}H_{20}N_2O_4$	320	C=63.75 H=7.50 N=8.75	C=63.52 H=7.36 N=8.96
93	Et	4'- thp	114-116	95.3	$C_{19}H_{24}N_2O_4$	348	C=65.52 H=8.05 N=8.05	C=65.74 H=7.83 N=8.31
94	Me	5'- thp	161-162	90.0	$C_{17}H_{20}N_2O_4$	320	C=63.75 H=7.50 N=8.75	C=64.03 H=7.21 N=8.94
95	Et	5'- thp	125-126	87.2	$C_{19}H_{24}N_2O_4$	348	C=65.52 H=8.05 N=8.05	C=65.86 H=7.76 N=7.91

† 2'-thp: 2'-(N-methyl-1',2',3',6'-tetrahydropyridyl);
4'-thp: 4'-(N-methyl-1',2',3',6'-tetrahydropyridyl);
5'-thp: 5'-(N-methyl-1',2',3',6'-tetrahydropyridyl)

disubstituted olefinic bond.

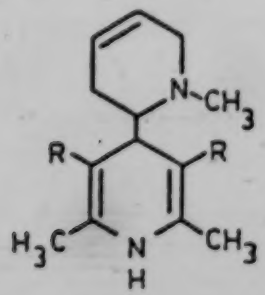


III

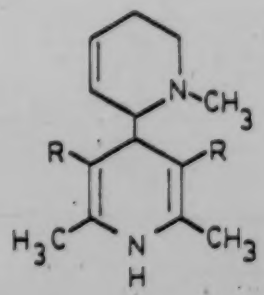


IV

The sodium borohydride reduction of the methiodide salts of 4-(2'-pyridyl)-1,4-dihydropyridines could yield two isomers of general structures V and VI. The ^{1}H nmr spectrum of the product obtained indicated that only isomer V (compounds 92 and 93) was formed.

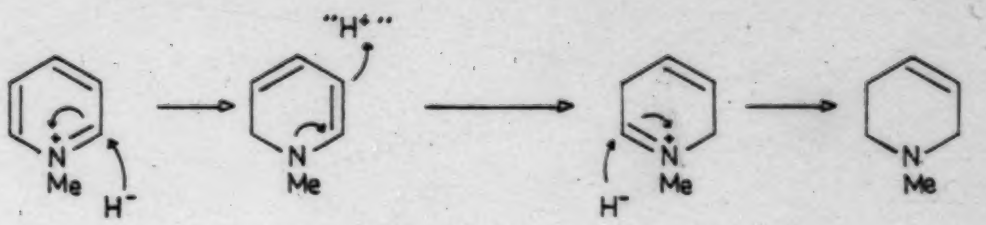


V



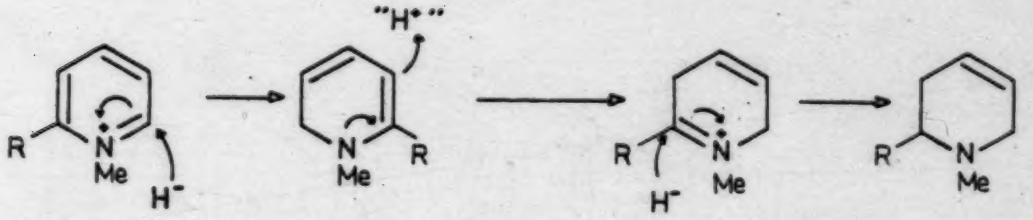
VI

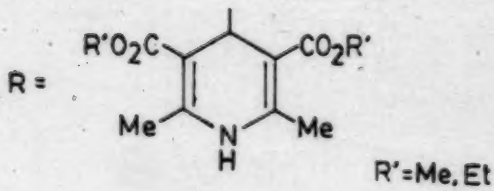
The mechanism for the sodium borohydride reduction of pyridinium iodides in protic media has been investigated [173,174]. This reduction involved the initial nucleophilic attack by hydride ion at a carbon vicinal to the quaternary nitrogen to afford an intermediate 1,2-dihydropyridine. Protonation of this intermediate followed by further attack by hydride anion yields the corresponding tetrahydropyridine (Scheme XIII).



SCHEME XIII

The same mechanism is likely operable for the formation of compounds 92 and 93. The formation of the products obtained may be explained assuming that initial attack by hydride ion occurs always at the 6'-position of the pyridinium ring as shown in Scheme XIV.





R'=Me, Et

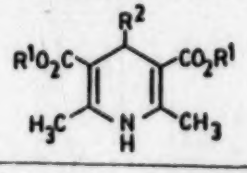
SCHEME XIV

This regiospecific hydride nucleophilic attack is likely due to steric hindrance exerted by the 1,4-dihydropyridine ring at the 2'-position of the pyridinium ring. After protonation of the intermediate 1,2-dihydropyridine occurs, hydride anion can only attack the C-2'position.

Characteristic ir bands and the ^{1}H nmr spectroscopic data are presented in Table XXIII. The N-H stretching bands appeared in the 3300 cm^{-1} range and the carbonyl ester groups displayed bands in the 1670 cm^{-1} region.

TABLE XXII

Spectroscopic Data for Dialkyl 2,6-dimethyl-4-[2'-(4-',5'-)[N-methyl-1',2',3',6'-tetrahydropyridyl]]-1,4-dihydropyridine-3,5-dicarboxylates



Comp.	R¹	R²§	ir, cm⁻¹ (CHCl₃)				¹H nmr, δ (CDCl₃)‡
			NH	C=C	CO_2R	C-N	
90	Me	2'-thp	3280	1630	1670	1280	1.7-1.9 and 1.9-2.06(two m,1H each,H-3'); 2.33(s,6H,=C-CH_3); 2.37(s,3H,NCH_3); 2.3-2.56(m,1H,H-2'); 3.12(m,2H,H-6'); 3.75 and 3.77(s,6H,CO_2CH_3); 4.3(d,J=7.72Hz,1H,H-4); 5.5-5.64(m,1H,H-5'); 5.64-5.8(m,J= ,=10Hz,1H,H-4') 6.38(s,1H,NH)†
91	Et	2'-thp	3285	1600	1680	1270	1.34(two overlapping t,J=6Hz,6H,$CO_2CH_2\underline{CH_3}$); 1.76-1.9 and 1.92-2.08(two m, 1H each,H-3'); 2.34 and 2.35(two s,6H,=C-CH_3); 2.38-2.5(m,1H,H-2'); 2.5(s,3H,NCH_3); 3.13(m,2H,H-6'); 4.23(two overlapping q,J=6Hz,4H,$CO_2\underline{CH_2}CH_3$); 4.36(d,J=8.88Hz,1H,H-4); 5.55(m,J= ,=10Hz,1H,H-5'); 5.7(m,1H,H-4'); 6.36(s,1H,NH)†
92	Me	4'-thp	3390	1600	1670	1285	2.12(m,2H,H-3'); 2.2(s,3H,NCH_3); 2.3 and 2.32(two s,6H,=C-CH_3); 2.42(t,J=5.5Hz,2H,H-2') 2.84(d,J=2.5Hz,2H,H-6'); 3.7(s,6H,CO_2CH_3); 4.49(s,1H,H-4); 5.38(m,1H,H-5'); 6.62(s,1H,NH)†
93	Et	4'-thp	3340	1630	1705	1300	1.3(t,J=6Hz,6H,$CO_2CH_2\underline{CH_3}$); 2.0-2.6(m,4H,H-2',H-3'); 2.3(s,9H,=C-CH_3,NCH_3); 2.9(m,2H,H-6'); 4.2(q,J=6Hz,4H,$CO_2\underline{CH_2}CH_3$); 4.55(s,1H,H-4), 5.4(m,1H,H-5'); 6.5(s,1H,NH)†
94	Me	5'-thp	3340	1630	1705	1280	2.1-2.2(m,2H,H-3'); 2.24(s,6H,=C-CH_3); 2.34(s,3H,NCH_3); 2.4(t,J=7.19Hz,2H,H-2'); 2.86(m,2H,H-6'); 3.6(s,6H,CO_2CH_3); 4.46(s,1H,H-4); 5.48(m,1H,H-4'); 6.06(s,1H,NH)†
95	Et	5'-thp	3425	1630	1705	1300	1.28(t,J=7.2Hz,6H,$CO_2CH_2\underline{CH_3}$); 2.14(m,2H,H-3'); 2.2(s,6H,=C-CH_3); 2.3(s,3H,NCH_3); 2.4(t,J=5.02Hz,2H,H-2'); 2.88(m,2H,H-6'); 4.06-4.32(m,4H,$CO_2\underline{CH_2}CH_3$); 4.49(s,1H,H-4); 5.49(m,1H,H-4'); 6.04(s,1H,NH)†

§ 2'-thp: 2'-(N-methyl-1',2',3',6'-tetrahydropyridyl); 4'-thp: 4'-(N-methyl-1',2',3',6'-tetrahydropyridyl); 5'-thp: 5'-(N-methyl-1',2',3',6'-tetrahydropyridyl)

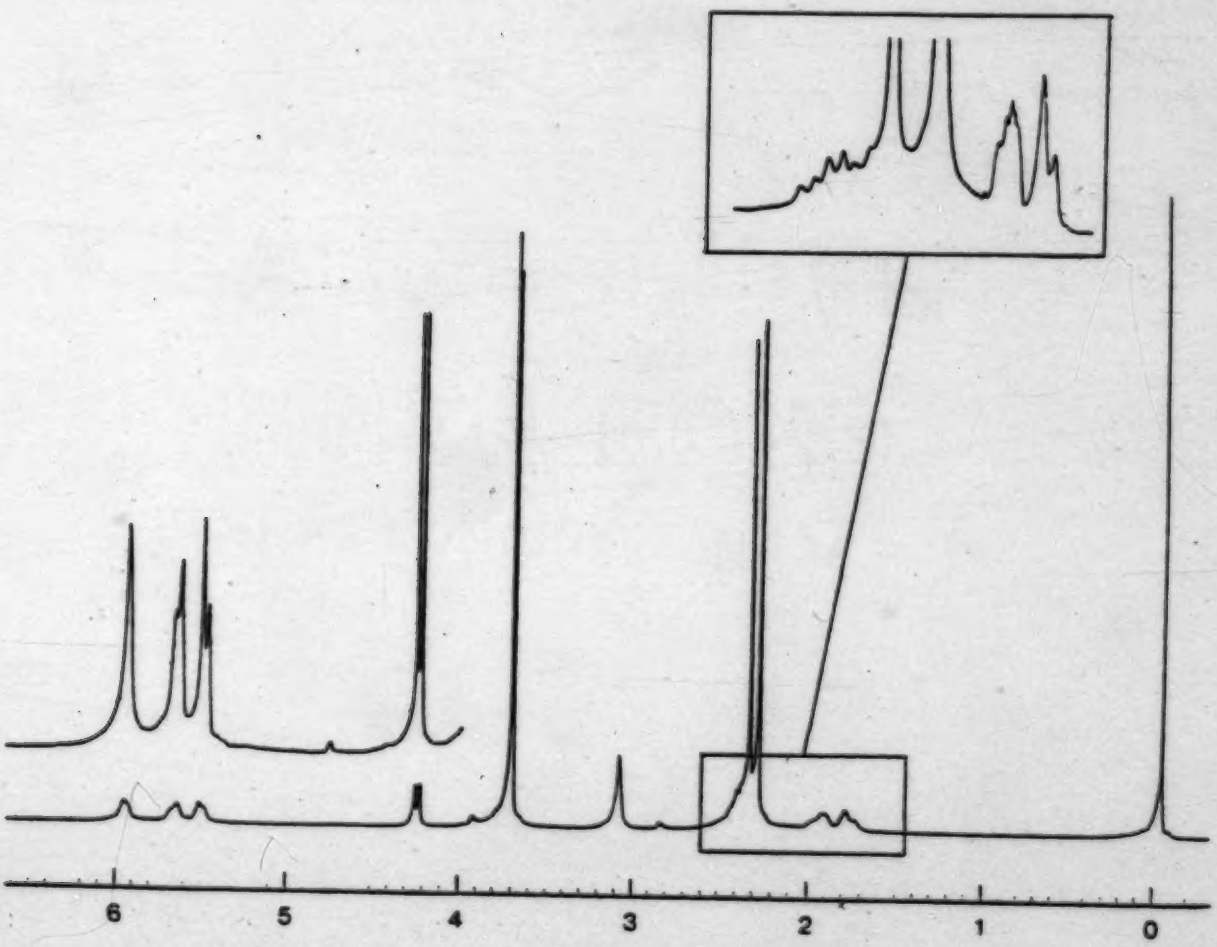
† Exchanges with D_2O

‡ Assignments confirmed by double irradiation experiments

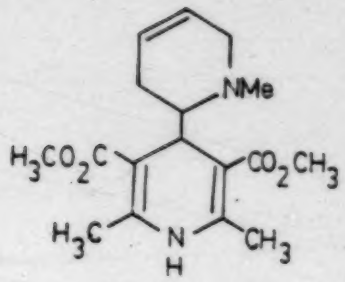
Protons attached to C-6' (vicinal to the tetrahydropyridyl nitrogen) appeared in the δ 2.84-3.13 range. They are deshielded relative to the C-2' protons which appeared at δ 2.0-2.6 due to the electron-withdrawing effect of the adjacent double bond.

Protons attached to the C-3' carbon atom appeared as multiplets at higher fields than all other tetrahydropyridine hydrogens in the δ 1.7-2.6 range. Vinylic hydrogens absorbed in the δ 5.38-5.8 range.

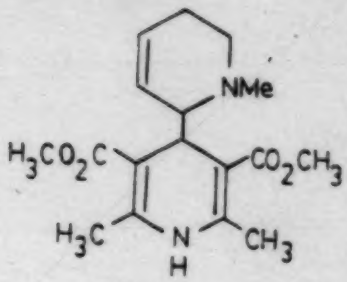
The structure assigned to compound 90 and a potential isomeric product 90a are shown below.



300 MHz spectrum ($CDCl_3$) of 90 (∂ 0-6)



90



90a

The ^1H nmr spectrum of this compound showed two multiplets at δ 2.3-2.56 and 3.12 which integrated for one and two hydrogens respectively. The chemical shifts indicated that these protons are vicinal to nitrogen. The spectrum also exhibited two multiplets at δ 1.8-2.0 attributed to the C-3' hydrogens. A doublet at δ 4.3 (J=7.72 Hz) was attributed to H-4. It is known that the allylic hydrogens attached to the 6-position of 1,2,3,6-tetrahydropyridines are deshielded relative to the C-2 protons[3]. Therefore, for the analogue 90 the multiplet at δ 3.12 must be due to the C-6' hydrogen atoms. The resonance signal at δ 2.3-2.56 corresponds to the C-2' proton. If the product was 90a then the proton labelled as H-6' (allylic and vicinal to nitrogen) should appear at lower field and integrate for only one hydrogen atom. However,the multiplet at lower field integrates for two hydrogens. The ^1H nmr spectrum of 90 agrees with these assignments. In additon, the doublet at δ 4.3 (due to the C-4 hydrogen) collapsed into a singlet upon irradiation of the resonance multiplet at δ 2.3-2.56. If the product was structure 90a decoupling of H-4 would have altered the signal due to the allylic proton vicinal to the nitrogen (*i.e.* H-6', at δ 3.12. These double irradiation experiments are consistent with structure 90.

A similar rationale was used for the structural assignment of diethyl 2,6-dimethyl-4-[2'-(N-methyl-1',2',3',6'-tetrahydropyridyl)]-1,4-dihydropyridine-3,5-dicarboxylate 93. The ^1H nmr spectrum of 91 showed two multiplets at δ 1.76-1.9 and 1.92-2.08 (H-3') and a third multiplet at δ 2.38-2.5 (H-2'). The C-6' protons appeared as a multiplet at 3.13 δ . The C-4 hydrogen appeared as a doublet at δ 4.36 (J=8.88 Hz). Decoupling experiments showed

that H-4 coupled to H-2'.

It was previously mentioned that the C-4 proton of compound 92 appeared as a doublet at δ 4.3. The coupling constant between H-4 and H-2' was 7.72 Hz. Vicinal coupling constants are influenced by the dihedral angle ø between the C-H bonds involved [173].The two parameters may be correlated using the Karplus equation[176,177]. The general form of the Karplus equation is shown below[178]:

$$J = A + B\cos\phi + C\cos 2\phi \qquad (1)$$

A, B and C are empirical constants with values of A 4.0; B -0.5, and C 4.5 [178]. The Karplus model is only useful to obtain the approximate magnitude of the dihedral angle ø and should be used with caution.

The dihedral angle between H-4 and H-2' in compound 92 may be roughly estimated from equation (1).Thus,

$$J = 4.0 - 0.5\cos\phi + 4.5\cos 2\phi \qquad (2)$$

but $$\cos 2\phi = 2\cos^2\phi - 1 \ [179] \qquad (3)$$

then $$J = 9\cos^2\phi - 0.5\cos\phi - 0.5 \qquad (4)$$

For the analogue 92,where J = 7.72 Hz, equation (4) then becomes:

$$9\cos^2\phi - 0.5\cos\phi - 8.22 = 0 \qquad (5)$$

The solution of equation (5) results in two possible values for the dihedral angle ø:

$$\phi_1 = 158.17^\circ$$

$$\phi_2 = 10.30^\circ$$

The approximate three-dimensional conformation and the Newman projection of 92 (ø=158.17°) are shown in Figures 6a and 6b, respectively.This conformational arrangement would be the most favored since it places the 1,4-dihydropyridine ring almost antiperiplanar to the tetrahydropyridyl moiety. A dihedral angle of 10.3° between the C-4 and C-2' hydrogens

would force the two heterocyclic rings into a *quasi* synperiplanar conformation. The non-bonded interactions between the two rings would be expected to increase. Therefore, it seems unlikely that the molecule would adopt a conformation where ø= 10.3°.

The dihedral angle between (CH)-4 and (CH)-2' was also estimated for 91 using equation (4). Equation (4) has only one solution when J=8.88 Hz. It assigns to ø an approximate value of 173.46°. The dihydropyridine 91 may then have a conformation similar to that proposed for the analogue 90.

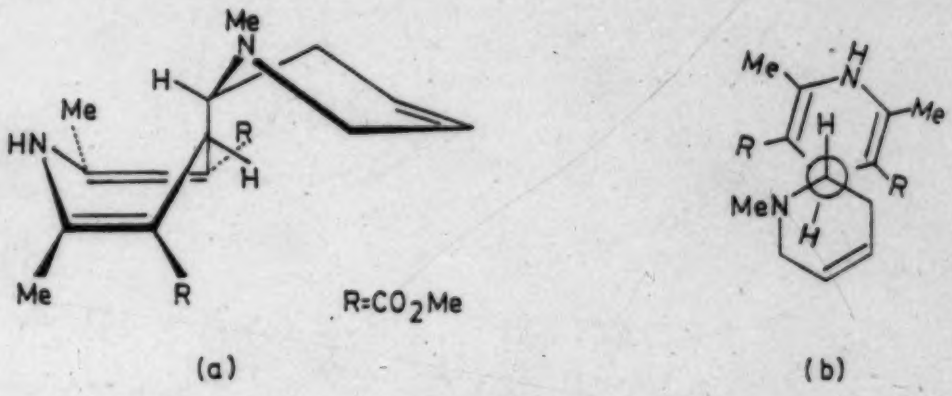


Fig. 6. Three-dimensional structure and Newman projection of 4-[2'-(1',2',3',6'-tetrahydropyridyl)]-1,4-dihydropyridine 90.

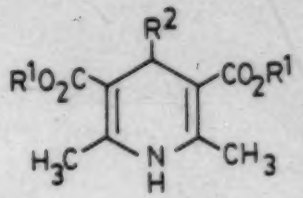
Pharmacological Activities of Dialkyl 2,6-dimethyl-4- [2'-(4'-,5'-)[N-methyl-1',2',3',6'-tetrahydropyridyl]]-1,4-dihydropyridine-3,5-dicarboxylates

The general structures of compounds 90-95 are shown in Figure 7. The ID_{50} values for the (4-tetrahydropyridyl)-1,4-dihydropyridines 90-95 are presented in Table XXIV. The pharmacological screening procedure was performed as described for compounds 30-41. The ID_{50} values observed for the analogues 90-95 are in the 10^{-5} M range.

The introduction of a tetrahydropyridyl substituent at C-4 of the 1,4-dihydropyridine ring has detrimental effects upon activity (*cf.* ID_{50} = 1.95 X 10^{-9} M for nifedipine and ID_{50} 10^{-7} M for (4-pyridyl)-1,4-dihydropyridines). A tetrahydropyridyl ring substituent may

TABLE XXIII

Inhibitory activities of Dialkyl 2,6-dimethyl-4-(2'-(4-',5'-)[N-methyl-1',2',3',6'-tetrahydropyridyl])-1,4-dihydropyridine-3,5-dicarboxylates on contractile responses to CD



Comp.	R^1	R^2†	$ID_{50}(M)$■
90	Me	2'-thp	$(6.7\pm0.1)X10^{-5}(2)$
91	Et	2'-thp	$(1.3\pm0.05)X10^{-5}(3)$
92	Me	4'-thp	$(2.3\pm0.1)X10^{-4}(2)$
93	Et	4'-thp	$(3.8\pm1.8)X10^{-4}(2)$
94	Me	5'-thp	$(2.9\pm0.2)X10^{-5}(2)$
95	Et	5'-thp	$(1.1\pm0.7)X10^{-4}(3)$

† 2'-thp: 2'-(N-methyl-1',2',3',6'-tetrahydropyridyl);
4'-thp: 4'-(N-methyl-1',2',3',6'-tetrahydropyridyl);
5'-thp: 5'-(N-methyl-1',2',3',6'-tetrahydropyridyl)

■ $ID_{50}\pm SD$. No. of experiments in parentheses.

exhibit a greater degree of puckering than a 1,2-dihydropyridyl and a pyridyl ring substituent. The π-electron density of a tetrahydropyridyl ring would be minimal since it has only one olefinic bond. The decreased activity for compounds 90-95 indicated that the conformation and/or degree of unsaturation of the 4-substituent in the 1,4-dihydropyridine ring may be important for calcium antagonistic activity, as previously suggested for the analogues with a 4-(1',2'-dihydropyridyl) substituent (*vide supra*).

In general, compounds having a C-3 and a C-5 ethoxycarbonyl group were more active than those with C-3 and C-5 methoxycarbonyl substituents. This agreed with previous results regarding the effect of the ester-substituent size upon activity.

The 4-[5'-(N-methyl-1',2',3',6'-tetrahydropyridyl)]-1,4-dihydropyridines 94 and 95 were more active than the 4-(4'-tetrahydropyridyl) analogues 92 and 93 These results agree once again with previous observations regarding the substituent position for the ring attached to C-4 of the 1,4-dihydropyridine .

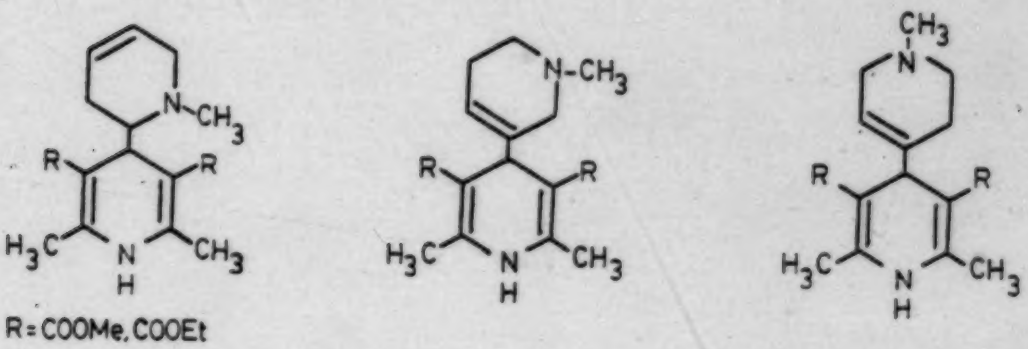


Fig. 7

Compound 95 was also more active than the 4-[2'-(N-methyl-1',2',3',6'-tetrahydropyridyl)]-1,4-dihydropyridine 91. This finding differs from previous test results for other nifedipine analogues. A substituent vicinal to the atom attached to the 1,4-dihydropyridine ring (as the nitro group of nifedipine) had always provided higher activity. Increased activity was assumed to result, at least in part, from the favourable

steric effect of the substituent on the overall conformation of the molecule.

The putative preferred conformation of dihydropyridines 90 and 91 has been discussed (*vide supra*). The 1',2',3',6'-tetrahydropyridyl ring in analogues 90 and 91 may be approximately coplanar with the 1,4-dihydropyridine ring. In addition, C-4' may be pointing away from the 1,4-dihydropyridine moiety.

The preferred conformation for the dihydropyridines 92-95 may be significantly different. The 1,4-dihydropyridine ring in these compounds is attached to an sp^3 carbon of the tetrahydropyridyl ring, rather than an sp^3 carbon, as in compounds 90 and 91. The tetrahydropyridyl ring may therefore be approximately perpendicular to the 1,4-dihydropyridine. The tertiary nitrogen would be expected to be positioned away from the 1,4-dihydropyridine ring. To decrease the non-bonded interactions between the C-3, C-4, and C-5 substituents, the 1,4-dihydropyridine ring may adopt a relatively planar conformation. The molecule would then have a spatial arrangement similar to the structure shown in Figure 8.

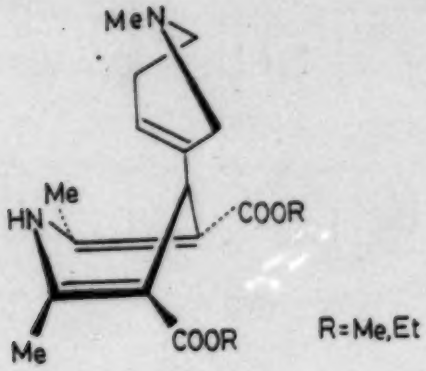
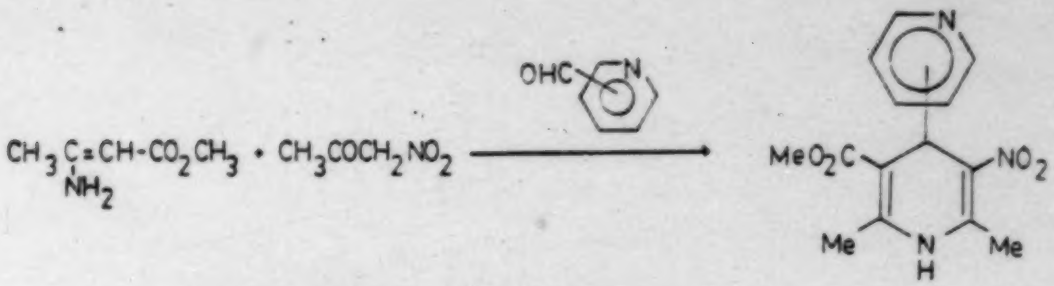


Fig. 8 Three-dimensional structure of 4-[5'-(1',2',3',6'-tetrahydropyridyl)]-1,4-dihydropyridines 94,95

If this hypothesis is valid, the preferred conformation of the analogues 92-95 may be similar to that of nifedipine, which may partially explain the increased activity of analogues 95 relative to 91 .

D. *Methyl 2,6-Dimethyl-3-nitro- 4-[2'-(3'-,4'-)pyridyl]1,4-dihydropyridine 5-carboxylates*

The analogues 96-98 possess a nitro group at the 3-position of the 1,4-dihydropyridine ring in place of an ester group which was present in all the nifedipine derivatives discussed previuosly.



SCHEME XV

Compounds 96-98 were prepared *via* the Hantzsch condensation of methyl-3-aminocrotonate with a pyridinecarboxaldehyde and 1-nitro-2-propanone (Scheme XV).

1-Nitro-2-propanone was synthetized by acetylation of nitromethane with N-acetylimidazolide[166]. Thus, nitromethane (1 mol, dried over 4-A sieves) was added slowly to a suspension of potassium t-butoxide (0.25 mol) in dry THF. Acetyl imidazolide (1 mol) in THF (50mL) was added dropwise with stirring. The resulting suspension was heated under reflux during 24 h. The mixture was allowed to cool to room temperature and filtered. The solid nitroenolate formed was washed with dichloromethane. Water was poured onto the salt and the nitropropanone was extracted with ethyl acetate after adjusting the pH of the mixture to 2-3 with concentrated hydrochloric acid. The combined organic extracts were dried with magnesium sulfate, the solvent was removed *in vacuo* and the solid nitropropanone (56% yield) was purified by recrystallization from THF. All attempts to acetylate nitromethane using conventional acetylating reagents such as acetyl chloride or acetic anhydride were unsuccessful. These reagents yielded products of O-acetylation which undergo subsequent polymerization

and/or decomposition.

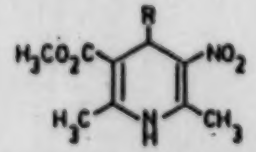
The Hantzsch condensation was carried out as described on page 26, except that the alkyl acetoacetate was replaced by nitropropanone. The 4-(3'-pyridyl)-1,4-dihydropyridine 97 analogue spontaneously precipitated from the reaction mixture. It was isolated by filtration and purified by elution from a silica gel column using hexane-ethyl acetate-acetonitrile (1:1.5:2.5 v/v/v) as eluant. The 2'- and 4'-pyridyl isomers were extracted from the crude reaction mixture with ethyl acetate. The oily residue obtained after solvent removal was dissolved in acetonitrile and the product precipitated upon addition of ethyl ether. The solid was purified by column chromatography using hexane-ethyl acetate-acetonitrile (1:1.5:2.5 v/v/v) as eluant.

Some physical data for the nitro-analogues 96-98 are shown in Table XXIV. The ir and ^{1}H nmr spectroscopic data are summarized in Table XXV. The ^{1}H nmr spectra exhibited two distinct singlets assigned to the methyl groups attached to C-2 and C-6 of the 1,4-dihydropyridine ring. The C-2 methyl group was deshielded approximately δ 0.3 relative to the C-6 methyl group, due to the electron-withdrawing effect of the nitro group present at C-3. The C-4 hydrogen was deshielded *ca.* δ 0.5 relative to nifedipine analogues having two ester groups at C-3 and C-5.

The 3-nitro-4-(3'-pyridyl)-1,4-dihydropyridine 97 was tested using the guinea pig longitudinal intestinal muscle. The procedure was identical to that described previously for testing calcium antagonistic activity. Preliminary results indicated that 97 is not a calcium channel inhibitor. In contrast, it promoted muscle contraction. A modified protocol, used for testing calcium antagonists (*vide supra*), was used to determine the concentration at which 97 produced half of the maximum contractile response. Compound 97 was administered in place of CD and the dose-response curve was determined. A calcium antagonist was not added during the experiment. The effective dose producing 50% of the maximum contractile response was 6.5 X 10^{-5}M. This result indicates that 97 may be a calcium channel agonist which promotes calcium entry into cells as Bay K8644 [153] (29a) and CGP 28392 [154] (29b).

TABLE XXIV

Physical Properties of Methyl 2,6-dimethyl-3-nitro-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-5-carboxylates

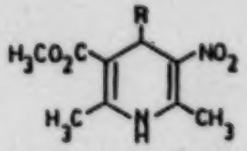


Comp.	R†	mp°C	%Yield	Formula	M.Wt.	Analysis(%) Calc.	Found
96	2'-py	192-194	15.2	$C_{14}H_{15}N_3O_4$	289	C=58.13 H=5.19 N=14.53	C=58.43 H=5.26 N=14.84
97	3'-py	199-201	30.2	$C_{14}H_{15}N_3O_4$	289	C=58.13 H=5.19 N=14.53	C=58.36 H=5.38 N=14.72
98	4'-py	208-210	7.8	$C_{14}H_{15}N_3O_4$	289	C=58.13 H=5.19 N=14.53	C=58.34 H=5.42 N=14.68

† 2'-py: 2'-pyridyl; 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl

TABLE XXV

Spectroscopic Data for Methyl 2,6-dimethyl-3-nitro-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-5-carboxylates



Comp.	R†	ir, cm^{-1} (CHCl$_3$) NH	CO$_2$Me	NO$_2$	^{1}H nmr, δ (DMSO-d$_6$)
96	2'-py	3160	1710	1512	2.03(s,3H,C6-CH$_3$); 2.4(s,3H,C2-CH$_3$); 3.55(s,3H,CO$_2$CH$_3$); 4.6(s,1H,H-4); 7.36(m,2H,H-3',H-5'); 7.83(d,J=8Hz of d,J=8Hz of d,J=1.5Hz,1H,H-4'); 8.7(d,J=6Hz of d,J=2Hz,1H,H-6'); 9.1(s,1H,NH)‡
97	3'-py	3192	1720	1512	2.03(s,3H,C6-CH$_3$); 2.3(s,3H,C-2CH$_3$); 3.5(s,3H,CO$_2$CH$_3$); 5.23(s,1H,H-4); 7.1-7.75(m,2H,H-5',H-4'); 8.26-8.5(m,2H,H-2',H-6'); 10.0(s,1H,NH)‡
98	4'-py	3192	1714	1512	2.0(s,3H,C6-CH$_3$); 2.33(s,3H,C2-CH$_3$); 4.53(s,1H,H-4); 7.2(d,J=5Hz,2H,H-3',H-5'); 8.56(d,J=5Hz,2H,H-2',H-6'); 9.4(s,1H,NH)‡

† 2'-py: 2'-pyridyl; 3'-py: 3'-pyridyl; 4'-py: 4'-pyridyl
‡ Exchanges with D$_2$O

IV. EXPERIMENTAL

Melting points were measured with a Büchi capillary apparatus and are uncorrected. Infrared spectra were recorded on a Unicam SP 1000 or a Nicolet 5DX spectrophotometer as potassium bromide discs or chloroform solutions. Proton nuclear magnetic resonance spectra were recorded for solutions in deuteriochloroform or DMSO-d_6, with tetramethylsilane as internal standard, on a Varian EM-360A or Brucker AM-300 spectrometer. Microanalytical results were within 0.4% of theoretical values. Flash column chromatography was carried out utilizing Merck 60 silica gel. Column chromatography was performed with JT Baker 60-200 mesh silica gel. Nitromethane was dried over 4-A sieves. Tetrahydrofuran was dried by refluxing with sodium metal and benzophenone. The solvent was subsequently distilled and used for the required reactions.

Preparation of Substituted Acetoacetates

General Procedure A: Sodium metal (6.9g, 0.3 mol) was added to a mixture of methyl acetoacetate (116g, 1 mol) and the required alcohol (2 mol). Dry toluene (150 mL) was added and the reaction mixture was heated under reflux for 12-16 h. The methanol formed during the reaction was removed by distillation as a toluene:methanol azeotrope. Excess toluene and alcohol were removed *in vacuo* and the product was isolated by distillation *in vacuo* .

Preparation of 2-(N,N-dimethylamino)ethyl acetoacetate: Sodium metal (13.8g, 0.2 mol) was added to N,N-dimethylethanolamine (89g, 1 mol) and the mixture was heated to 70-80°C. When all sodium metal had dissolved, diketene (86g, 1 mol,50% acetone solution) was added dropwise. The temperature of the reaction mixture was maintained between 70 and 80°C for 24 h. The crude acetoacetate was used for the next reaction (Hantzsch Condensation) since distillation resulted in partial decomposition. Yield 82.7g(47.8%), bp 140°C/3mm (lit.[164]: 103°C/2mm), ^{1}H nmr ($CDCl_3$): δ 2.0(t,J=6Hz, 2H,$CH_2CH_2N(CH_3)_2$); 2.1(s,3H,CH_3CO);

2.5(s,2H,CO-CH_2-CO); 4.2(t,J=6Hz, $OCH_2CH_2N(CH_3)_2$).

Preparation of Methyl 3-aminocrotonate

Ammonium hydroxide (105g, 3 mol, NH_3 soltn. content 30%) was added to a solution of methyl acetoacetate (116g, 1 mol) in water (50 mL) at room temperature. The reaction mixture was stirred at room temperature for 4-5 h and the product was filtered and recrystallized from ethanol. Yield 114g (99%), mp 82-84°C (lit.[144]: 83-85°C); ^{1}H nmr ($CDCl_3$): δ2.0 (s,3H,CH_3CO); 2.26(s,2H,$COCH_2C=NH$); 3.6 (s,3H,CO_2CH_3); 4.5(s,1H,NH).

Preparation of Acetyl Imidazolide

Acetyl chloride (78.5g, 1 mol) was added dropwise to a solution of imidazole (136g, 2 mol) in 250 mL dry tetrahydrofuran at room temperature. The reaction was stirred at room temperature for 4-6 h and the imidazolium chloride formed was filtered. The filtrate contained the acetyl imidazolide. The solvent was removed *in vacuo* The crude imidazolide was recrystallized from tetrahydrofuran. Yield 177g (99.2%), mp 103-105°C (lit.[181] 104°C); ^{1}H nmr ($CDCl_3$): δ2.4(s,3H,$COCH_3$); 7.26(m,2H,H-4,H-5); 7.86(s,1H,H-2)

Preparation of 1-Nitro-2-propanone

Nitromethane (71g, 1 mol) was added dropwise to a suspension of potassium t-butoxide (28g, 0.25 mol) in dry tetrahydrofuran(200 mL). Acetyl imidazolide (178g, 1 mol) was added dropwise with stirring. The resulting suspension was heated under reflux for 24 h prior to cooling to room temperature. The crude enolate salt was separated by filtration and washed with dichloromethane. Water (100 mL) was poured onto the salt and the pH of the solution was adjusted to 2-3 with concentrated hydrochloric acid. The suspension was extracted

with ethyl acetate while maintaining the pH at 2-3 by addition of hydrochloric acid. The organic extracts were dried($MgSO_4$) and the solvent was removed *in vacuo* . The crude product was purified by recrystallization from methanol. Yield 63.3g (56%), mp 37-38°C (lit.[180]: 40°C); ^1H nmr ($CDCl_3$): δ2.2(s,3H,CH_3CO); 5.5(s,2H,CH_2NO_2).

Preparation of t-Butylchloroformate

Potassium t-butoxide (11.2g, 0.1 mol) was added to a solution of phosgene (9.9g, 0.1 mol,12.5% soln. in benzene) in ethyl ether (40 mL) precooled to -65°C. The reaction was allowed to proceed for 4 h. This solution ot t-butylchloroformate was maintained at -65°C to avoid decomposition prior to use in subsequent reactions.

Preparation of 3-Alkyl-5-methyl-2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates (30-41)

The alkyl acetoacetate (0.1mol) was added to a solution of 2-(3-,4-)pyridinecarboxaldehyde (10.7g, 0.1 mol) in ethanol (50 mL) and then methyl-3-aminocrotonate (8.9g, 0.1mol) was added with stirring.The reaction mixture was heated at reflux for 12-16 h and then poured onto crushed ice(100 mL). The crude product was separated from the mixture by filtration or by extraction with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The solid dihydropyridine obtained was purified by elution from a silica gel column (5cm X 65cm) using ethyl acetate-acetone (9:1 v/v) as eluant. This general procedure was altered for the isolation of some derivatives. The modifications introduced are presented below.

Purification of 3-i-propyl-5-methyl-2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates was achieved by flash chromatography using

hexane-ethyl acetate-ethyl ether (1:1:1 v/v/v) as eluant. This solvent system provided a good separation of the desired products (31,35,39) from the diisopropyl and dimethyl dicarboxylates formed as by-products, which were eluted from the column before and after the desired product, respectively.

Purification of 3-isobutyl-5-methyl-2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates was carried out by elution from a silica gel column(5cm X 65cm) using a mixture of ethyl acetate and hexane (1:1 v/v) as eluant.

Preparation of Dialkyl 2,6-dimethyl- 4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates (42-53)

The alkyl acetoacetate (0.2 mol) was added to a solution of 2-(3-,4-)pyridinecarboxaldehyde (10.7g, 0.1 mol) in ethanol (50 mL), followed by addition of ammonium hydroxide (14g, 0.4 mol, NH_3 solution content 30%) with stirring. The yellow mixture was heated under reflux for 12-16 h and poured onto crushed ice (100 mL). The product was separated and purified as described previously for 3-alkyl-5-methyl-2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates 30-41.

The diisopropyl and diisobutyl 2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylates 43,44,47,48,51,52 were purified by elution from a silica gel column (5cm X 65cm) using ethyl acetate-hexane (7:3 v/v) as eluant.

Preparation of Methyl 3-cyano-2,6-dimethyl-4-[3'-(4'-)pyridyl]-1,4-dihydropyridine-5-carboxylates (54,56)

3-Aminocrotononitrile (8.2g, 0.1 mol) was added to a solution of 3-(4-)pyridinecarboxaldehyde (10.7g, 0.1 mol) and methyl-3-aminocrotonate (8.9g, 0.1 mol) in ethanol (50 mL) with stirring. The mixture was heated under reflux for 24 h. The reaction mixture was poured onto crushed ice (100 mL) and the solid product that separated was filtered. Purification was effected by elution from a silica gel column (5cm X 65cm) using acetone-hexane (2:3 v/v) as eluant.

Preparation of 3,5-Dicyano-2,6-dimethyl-4-[3'-(4'-)pyridyl]-1,4-dihydropyridines (55,57)

A solution of 3-(4-)pyridinecarboxaldehyde (10.7g, 0.1 mol) and 3-aminocrotononitrile (17.8g, 0.2 mol) in ethanol (50 mL) was heated under reflux for 24 h. The product was isolated and purified as described previously for the 3-cyano-1,4-dihydropyridine-5-carboxylates 54 and 56.

Preparation of Methyl

2,6-dimethyl-3-nitro-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-5-carboxylates (96-98)

1-Nitro-2-propanone (10.3g, 0.1 mol) was added to a solution of 2-(3-,4-)pyridinecarboxaldehyde (10.7g, 0.1 mol) and methyl-3-aminocrotonate (8.9g, 0.1 mol) in ethanol (100 mL) with stirring. The reaction mixture was heated under reflux for 24 h and was poured onto crushed ice (100mL).

The 3'-pyridyl derivative was separated by filtration and purified by elution from a silica gel column (7cm X 80cm) using hexane-ethyl acetate-acetonitrile (1:1.5:2.5 v/v/v) as eluant.

The 2'- and 4'-isomers were extracted from the crude reaction mixture with ethyl acetate (150mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo* . The oily residue obtained was dissolved in acetonitrile. The crude product

precipitated upon addition of ethyl ether. The crude dihydropyridines were then purified by elution from a silica gel column (7cm X 80cm) using hexane-ethyl acetate-acetonitrile (1:1.5:2.5 v/v/v) as eluant.

Preparation of Dialkyl (3-alkyl-5-methyl-) 2,6-dimethyl-4-{3'-(4'-)[N-alkoxycarbonyl-1',2'-(1',6'-)-dihydropyridyl]}- 1,4-dihydropyridine-3,5-dicarboxylates (58-85)

Sodium borohydride (1.9g, 0.05 mol) was added to a solution of dialkyl(3-alkyl, 5-methyl) 2,6-dimethyl-4-[3'-(4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylate (0.01 mol) in methanol (20-40 mL) precooled to -65°C. After 10 min, a solution of alkyl(aryl)chloroformate (0.015 mol) in dry ether (5-10 mL) was added dropwise with stirring. The reaction was allowed to proceed for 4-6 h at -65°C with stirring. The mixture was poured onto crushed ice (50 mL) and was allowed to come to room temperature. The crude product was isolated by filtration or by extraction with dichloromethane. The organic extracts were dried ($MgSO_4$) and the solvent was evaporated *in vacuo* . The solid 1',2'-(1',6'-)dihydropyridyl product was purified by flash chromatography (column size: 3cm X 25cm) utilizing hexane-ethyl acetate (1:1 v/v) as eluant.

The sodium borohydride reduction of 4-(3'-pyridyl)1,4-dihydropyridines afforded mixtures of 1',2'- and 1',6'-dihydropyridyl derivatives which could not be separated by column or thin layer chromatographic techniques. The ratio of the two isomers obtained was determined by ^1H nmr spectroscopy, using the integration of selected resonance signals.

Methyl 3-cyano-2,6-dimethyl-4-{3'-(4'-)[N-alkoxycarbonyl-1',2'-(1',6'-)dihydropyridyl]}-1,4-dihydropyridine-5-carboxylates (73-76) were prepared and purified following a similar general procedure.

Preparation of Dialkyl 2,6-dimethyl-4-[2'-(4'-,5'-)[N-methyl-1',2',3',6'-tetrahydropyridyl]]-1,4-dihydropyridine-3,5-dicarboxylates (90-95)

A solution of diethyl (dimethyl) 2,6-dimethyl-4-[2'-(3'-,4'-)pyridyl]-1,4-dihydropyridine-3,5-dicarboxylate (0.01 mol) in acetone (50 mL) was added to iodomethane (4.25g,0.03 mol) and the mixture was heated under reflux for 7-9 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo* . The pyridinium iodide was dissolved in 20 mL ethanol-water (1:1 v/v) and cooled to 0°C. This solution was then added to a solution of sodium borohydride (1.9g, 0.05 mol) in absolute ethanol (15 mL) precooled to 0°C. The reduction was allowed to proceed for 5-7 h at 0°C. Water (50 mL) was added and the solid product was isolated by filtration. The product was purified by recrystallization from aqueous ethanol (1:1 v/v, 10 mL).

Tissue Preparations and Determination of ID_{50}values

The ID_{50} values for some of the calcium antagonists prepared were determined by F. Li Kwong Ken under the supervision of Dr. M. Wolowyk.

The procedure was a modification of the experimental protocol reported by Triggle *et al.* [163] as described below.

Male albino guinea pigs (body weight 300-450 g) were sacrificed by decapitation. The intestine was removed above the ileo-caecal junction. Longitudinal smooth muscle segments of 2 cm length were mounted under a resting tension of 300-400 mg. The segments were maintained at 37°C in a 10-mL jacketed organ bath containing oxygenated (100% O_2) physiological saline solution of the following composition(mM): NaCl: 137; $CaCl_2$: 2.6; KCl: 5.9; $MgCl_2$: 1.2; glucose: 11.9, buffered by Hepes-NaOH to pH 7.4.

The muscles were equilibrated for 1 h with a solution change every 15 min. Two successive control contractions were elicited at 15-min intervals with $5X10^{-7}$M cis-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (CD). The isometric

contractions were recorded with a force displacement transducer (FT 03C) on a GRASS physiograph.

The mean of the two contractile responses was taken as the 100% value for the tonic (slow) component of the response. The muscle was washed with Hepes saline solution and was allowed to re-equilibrate.

The calcium antagonist was added ten minutes before the dose-response for CD was determined. The drug-induced inhibition of contraction was expressed as percent of control. The ID_{50} values were graphically determined from the concentration-response curves.

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